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ERRATUM

Footnote 1 at the bottom of page 145 of the *Bulletin of the Johns Hopkins Hospital*, Vol. LII, No. 2, February, 1933, should read as follows:

"Aided in part by a grant from the Committee on Research in Syphilis, Inc., and by a grant from the Committee on Scientific Research of the American Medical Association."

CRYSTALLINE INSULIN IN THE TREATMENT OF DIABETES MELLITUS[1]

JOHN EAGER HOWARD, M.D. AND AGNES DE LAWDER

From the Departments of Medicine and Pharmacology, Johns Hopkins University and Hospital

It is important from a practical as well as from a scientific point of view to know whether crystalline insulin, first prepared by Abel and his co-workers in 1926 (1), will give the therapeutic effects obtained by the injection of commercial insulin into patients suffering from diabetes mellitus. In so far as we are aware, no well controlled clinical trial has ever been made of this crystalline substance. Gauged from animal experiments crystalline insulin produces the usual physiologic effects, *i.e.*, hypoglycemia when injected into normal animals. To test the efficacy of this preparation in human diabetics four patients were treated alternately with crystalline insulin and a standard commercial preparation of insulin (Iletin, Lilly).

PREPARATION OF THE MATERIAL

Crystalline insulin which had been several times recrystallized and was, therefore, of very high purity was prepared in the Department of Pharmacology of the Johns Hopkins University. The physiological activity of such crystals, as assayed on rabbits, is 24 international units per milligram (2). The solutions of crystalline insulin employed in the present series of experiments were practically equivalent in unitage to the commercial preparations used. In view of the fact that the first solutions, which were prepared by dissolving the crystals in distilled water, caused pain at the site of injection, physiological salt solution was subsequently employed as the solvent. Briefly, a known quantity of crystalline insulin was weighed out on a micro-balance; a few drops of N/20 hydrochloric acid were added to dissolve the crystals, and sterile saline was added to the desired amount. Such solutions caused no discomfort to the patients.

[1] Submitted for publication June 14, 1932.

TYPES OF PATIENTS

For this study four patients of different types of diabetes were selected: (1) a 12-year old Jewish boy with relatively mild diabetes of only one month's duration; (2) a white boy of 21 with moderately severe diabetes of at least one year's standing; (3) a white girl of 24 with diabetic symptoms of three months' duration, which had become manifest just at the end of pregnancy; and (4) an elderly white man of 64 with known long-standing diabetes of moderate

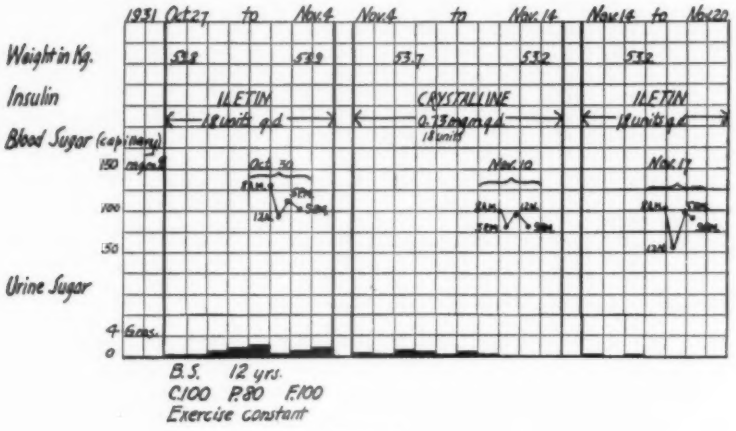


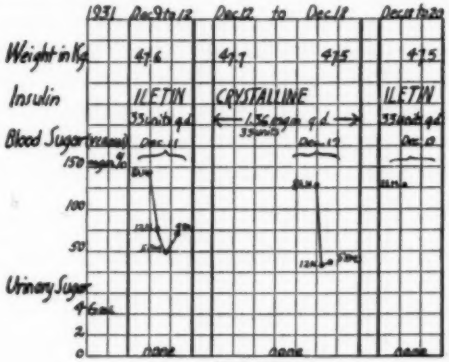
CHART 1

severity. In so far as could be determined there were no complicating disease factors in any of the patients during the period of the experiment.

PROCEDURE

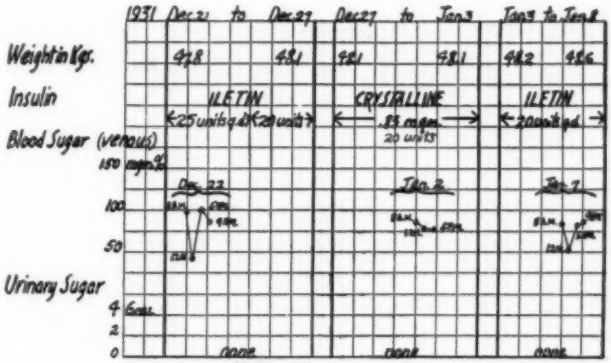
The procedure was as follows: each patient was carefully standardized by diet and commercial insulin. When the blood-sugar curves (estimates being made at 4-hour intervals during the day, *i.e.*, before meals and at 9:00 P.M.) were found to be stabilized within normal limits, crystalline insulin was substituted for the commercial preparation without the patient's knowledge. After crystalline insulin had been used for periods varying from five to seven days, another "all-

day" blood sugar estimation was done. During the entire period of observation there was no alteration whatever in each patient's diet or



T. P. 21 yrs.
C. 135 P. 70 F. 100
Exercise constant

CHART 2



M. F. 20 yrs.
C. 140 P. 60 F. 110
Exercise constant

CHART 3

conditions of daily routine. All diets were prepared in the kitchen of the Metabolism Ward of the Johns Hopkins Hospital under the personal supervision of Miss Mildred Struve.

RESULTS

In the elderly patient whose diabetes was of long standing almost identical "all-day" sugar curves were obtained while the commercial insulin and the crystalline insulin were being used. A decrease of two units was made while on crystalline insulin because of mild mid-day reactions (See Chart 4). In the other three patients, however, whose diabetes was of more recent origin, the "all-day" curves tended steadily downward under crystalline insulin, *i.e.*, the blood sugar tended to be

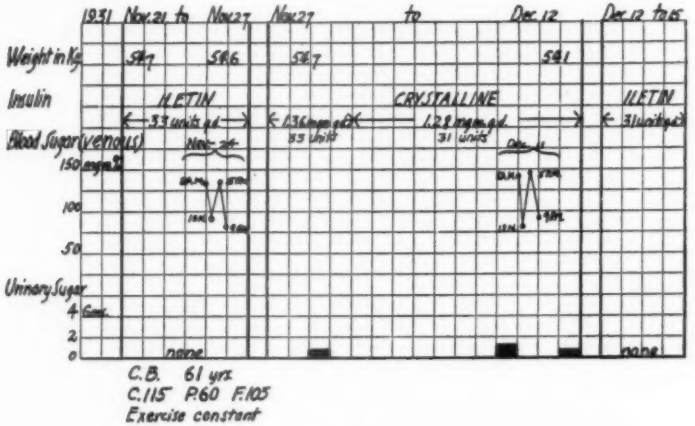


CHART 4

at lower levels toward the end of the periods of observation. This was interpreted as being due to the increasing carbohydrate tolerance which usually occurs in the patients under careful regulation. That it could not have been due to underestimation of the potency of the crystalline insulin is evident from the fact that the curves continued downward even after the patients had been changed back to commercial insulin.

A single protocol only will be given as an example of the method used and in explanation of the charts.

CASE REPORT

Case 1. A 12-year old Jewish schooolboy, rather precocious in school and slightly over weight. No family history of diabetes. He had undergone a ure-

throtomy seven years previously in Johns Hopkins Hospital for congenital urethral defect which had brought about obstruction. Enuresis had been present until nine years of age. His general health had been excellent, but he had always indulged heavily in sweets and starchy foods. In September, 1931, following a coryza and cough of one week's duration, the patient suddenly developed polyuria with moderate polydipsia and began to lose weight. He was seen in the diabetic clinic of the Johns Hopkins Hospital one month after the onset of symptoms. A heavy trace of sugar was found in the urine. He was started on a diet of carbohydrate 100, protein 80, fat 165 (40 calories per kilo). Glycosuria continued, however, and one week later, on October 21, 1931, he was sent into the hospital for 'regulation.' At the time of admission his urine showed 3 per cent of sugar with traces of acetone and diacetic acid. The urinary findings were otherwise normal. The fasting blood sugar the next morning 210 mgm. per cent. Weight 54.9 kilograms (a loss of 4 kilograms during the preceding month). Physical examination revealed no abnormal features except for slight overnutrition. Blood pressure normal. Hemoglobin, red blood cells and white cells normal. X-ray of chest showed the lungs to be clear. Blood Wassermann reaction negative. The patient was afebrile and completely symptom-free throughout his course in the hospital.

He was put on a diet of carbohydrate 100, protein 80, fat 100 (29.5 calories per kilogram of body-weight), the diet being divided equally into thirds. From October 27 to November 3 with commercial insulin in doses of 10 units 20 minutes before breakfast and 8 units 20 minutes before supper, he was essentially sugar-free (see chart 4), the total sugar excretion per 24 hours varying between 0.6 gm. and 3.3 gm. A blood-sugar curve was done on October 31, samples of blood being obtained before each meal and at 9:00 P.M. This curve read in milligrams 134–89–116–102 per cent.

On November 4 substitution of crystalline insulin in equivalent doses was begun. As may be seen in the chart the patient's condition remained unaltered. Very small amounts of glucose were excreted in the urine for seven days, after which the urine became entirely sugar-free. The patient was continued on crystalline insulin for a period of ten days and on the ninth day blood sugar determinations were again made before meals and at 9:00 P.M. These estimations were somewhat lower throughout than those taken twelve days before when the patient was receiving commercial insulin, and agreed with the clinical evidence that the patient now had no sugar in the urine. The lower blood-sugar levels and the disappearance of glycosuria might be interpreted in one of two ways: (1) slight underestimation of the potency of crystalline insulin, or (2) increasing carbohydrate tolerance on the part of the patient. That the latter was probably the case seems to be indicated by the "all-day" sugar curve done on November 17 when the patient had been back on commerical insulin four days. This curve averaged slightly lower than that of November 11. Furthermore, since his discharge from the hospital the patient's insulin has been reduced, and two months later on exactly similar diet he was aglycosuric, taking only 8 units before breakfast and 6 units before supper. His weight was approximately stationary throughout his stay in the hospital.

The course of the other patients were similar to the above case and can be followed in the charts. For the sake of brevity complete protocols will not be given. As noted above, in all the patients there was a slight tendency to an increase of carbohydrate tolerance during the periods of observation.

SUMMARY

A series of four diabetic patients were regulated on diets and commercial insulin under most careful supervision. Crystalline insulin was then substituted for the commercial insulin in equivalent doses.

Apart from slight increases in carbohydrate tolerance, which might be expected in diabetic patients under treatment, no appreciable difference could be detected clinically between the periods during which commercial insulin and crystalline insulin were injected.

CONCLUSION

Crystalline insulin gives the same therapeutic effects as commercial preparations of insulin when injected in equivalent doses into human subjects suffering from diabetes mellitus.

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(2) JENSEN, WINTERSTEINER AND GEILING: *ibid.*, 1929, xxxvi, 115.

EXPERIMENTS DEMONSTRATING THAT ACQUIRED IMMUNITY IN SYPHILIS IS NOT DEPENDENT UPON ALLERGIC INFLAMMATION[1]

ARNOLD R. RICH, ALAN M. CHESNEY AND THOMAS B. TURNER

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It has been known for twenty years that allergy plays a rôle in syphilis as it does in so many, if not in all, bacterial infections. In 1911 Noguchi (1) showed that rabbits could be rendered allergic to emulsions of dead spirochaetes, and shortly afterwards it was demonstrated that syphilitic human beings likewise react to the spirochaetal emulsion. The reaction, which is spoken of as the "luetin test" and which is analogous to the tuberculin test, is positive especially during the tertiary stage of syphilis, much less frequently during the secondary stage, and only very rarely if ever during the primary stage. Hypersensitiveness in syphilis, therefore, is ordinarily not well developed before the tertiary stage; and, indeed, this might have been inferred from the pathological aspects of the disease, for bacterial allergy means that the body has become altered in such a manner that the tissues are more susceptible to injury by the organisms in question, and it is in the tertiary stage that the spirochaetes, which have been harbored in the body for months with relatively little effect, begin to produce caseous necrosis and extensive destruction of tissue.

The accelerated and exaggerated inflammation which characterizes the allergic reaction, and which results from the enhanced susceptibility of the tissues to the injurious effects of the invading organisms, is widely regarded as an essential part of the mechanism of acquired immunity. This view has been held in regard to bacterial infections in general, and it has been unhesitatingly applied by numerous writers to syphilitic infection. In the literature it is not uncommon to encounter such statements as the following:

[1] Submitted for publication October 17, 1932.

"(Early) treatment with salvarsan . . . . prevents the development of the tertiary stage, and the patients are, therefore, cured before they have reached the stage of allergy. It is to this that one must attribute the increasing number of reinfections noted during recent years" (2).

Again, in a recent text-book on hypersensitiveness and immunity (3) it is stated flatly that

"the relative immunity (in syphilis) is really a hypersensitiveness. . . . . Persons with syphilis are protected from reinfection by the local hypersensitive reaction which occurs at the seat of reinoculation."

In regard to such statements which postulate the necessity of allergy for the operation of immunity in syphilis, while it is quite true that reinfections are more frequent in cases in which the first infection is treated early, it by no means follows that this has anything to do with allergy. Indeed, the very fact that reinfections are exceedingly rare in untreated cases even in the primary stage in which, as we have said, allergy is not manifest, should make one realize that some factor other than allergy lies at the bottom of the matter. Furthermore, there is an old clinical observation long antedating the luetin test which hardly squares with the view that the mechanism of protection in syphilis is a local hypersensitive reaction. More than a hundred years ago it was discovered that persons in the primary stage of syphilis are refractory to the inoculation of material from their own chancres. When such reinoculations are made, the result is not an exaggerated lesion such as characterizes an allergic reaction but, rather, no appreciable lesion of any sort. Since similar autoinoculation with the material from a soft chancre (Ducrey's bacillus) regularly produces a second soft chancre at the new site, this procedure was widely used by clinicians in the past century as a diagnostic method for the differentiation of the chancre from the chancroid. The thousands of such inoculations made for this purpose really represent highly interesting experiments upon human beings, and they serve to indicate that in the human being immunity is present in the absence of allergy as early as the primary stage of the disease. The literature on this question has been discussed in detail by one of us in another place (4). These inoculations were, of course, not performed under carefully controlled conditions from the standpoint of hypersensitiveness. The

present experiments were, therefore, carried out in order to study pointedly the tissue reactions of the immune body following reinfection.

EXPERIMENTS

The studies herein reported were carried out in four separate experiments. The essential features of all the experiments were as follows. Rabbits were first inoculated with syphilis in such a manner as to produce characteristic evidences of the disease. After varying lengths of time these animals, along with controls, were inoculated intradermally with an homologous strain of *Treponema pallidum* and were carefully observed, first, for evidences of an allergic reaction at the site of reinoculation and, second, for evidences of immunity to the reinoculation.

Although the experiments will be tabulated separately, certain conditions obtaining in each will be cited at this point to avoid repetition.

The Nichols strain of *T. pallidum* was used for both first and subsequent inoculations. The first inoculation was made in one of several ways—testicular, intravenous, subcutaneous, intracutaneous, or by deposition of the virus on the surface of a granulating wound. In any case, however, only animals which showed definite evidences of infection as a result of the first inoculation were used in the experiments. Some animals were given antisyphilitic treatment before the test inoculation. Treatment when given was begun approximately six months after the first inoculation, and consisted of six intravenous injections of arsphenamine, 20 mgm. per kilogram of body-weight, at weekly intervals. The test inoculations were never made until many days after the last dose of arsphenamine.

The test inoculation in each case was made by intracutaneous injection of the virus in two areas on the rabbit's back. The virus for this inoculation was prepared under aseptic precautions by emulsifying a portion of a syphilitic testis and then centrifugalizing the emulsion. The supernatant fluid which was used for the injections was free from gross tissue particles and was always rich in actively motile *Treponemata pallida*. The skin of the animal's back was rendered free from hair by shaving, or by the use of a depilatory mix-

ture, the chief ingredient of which was barium sulphide. Of the inoculum 0.1 cc. was injected intradermally on each side and the sites of inoculation were carefully marked in order that they could be readily identified at a later date even in the absence of tissue reaction. As controls, normal rabbits were inoculated in the same manner with the same virus at the same time.

Following the test inoculations all animals were examined daily for the first week, biweekly for another two weeks, and once weekly thereafter for any evidence of an allergic reaction at the site of inoculation, and for the occurrence of local or generalized syphilitic lesions. At various intervals following the test inoculations an inoculated area was excised from a test and also from a control animal for microscopic study. In each instance care was taken to select the area showing the most marked changes on that particular day. The site of inoculation on the opposite side was left undisturbed so that it was possible to determine the presence or absence of a chancre immunity in the animal. In each instance a number of microscopic sections were made through the point of inoculation and through the adjacent tissue on each side of the sites removed for examination so that the region of most pronounced reaction could be studied.

Expt. I. In this experiment fifteen rabbits, immunized by infection, were reinoculated intracutaneously and the sites of inoculation were observed for the appearance of an allergic reaction. All the animals, which previously had shown characteristic evidences of syphilitic infection, were at the time of reinoculation well past the period when further active lesions usually occur; about half the number had been infected 288 days and the other half 188 days. The first inoculation was intratesticular in six, intravenous in five, and subcutaneous in four. No treatment was given at any time. Six of the animals were males and eight females. As controls for the test inoculation, fifteen normal rabbits were inoculated intracutaneously with the same virus. Each animal in both series was inoculated in two places so that one site could be removed for microscopic study, the other being left for subsequent observation.

Twenty-four hours after the test inoculation, several animals in the test and also in the control group showed a faint erythema at the site of inoculation. This reaction was very mild, and in no instance

was greater in the test than in the control animals. By the third day it had completely subsided. Many of the animals in each group showed no reaction whatever. The skin of the test animals remained completely normal in appearance for the rest of the period of observation, while in all of the controls a lesion was detectable by the tenth day, and within a week or two a characteristic chancre had developed. An inoculated area from a test and from a control animal was excised for microscopic study on the first, second, third, fourth, fifth, sixth, tenth, twentieth, twenty-eighth, and forty-first day. A description of these sections is given in Appendix A. Suffice it to say that neither macroscopically nor microscopically was there any evidence whatever of an allergic reaction in the test animals, although quite clearly these animals were immune, as was shown by their failure to develop chancres or metastatic lesions (See Figs. 1–8). The result was uninfluenced by the method of first infection, and no difference was noted between the animals inoculated 288 days and those inoculated 188 days after the first infection (see Table I).

Expt. II. This experiment was devised primarily to determine whether in rabbits the duration of the first infection plays any rôle in the immediate response to reinoculation. The test animals, thirty-five in number, may be divided into four groups, A, B, C and D, corresponding to the lapse of time between the first and test inoculations. For Group A, composed of eight rabbits, this was 482 days; for Group B, six rabbits, 415 days; for Group C, eight animals, 314 days; for Group D, thirteen animals, 128 days. The animals in Groups A, B and C were well past the period of active syphilitic lesions, while in all but two rabbits of Group D the syphilitic infection had reached a period of latency. In two rabbits the chancre resulting from the first inoculation had not quite healed. The animals in Group A were given antisyphilitic treatment six months after the first inoculation, but none of the other rabbits were treated. It will be noted that the animals composing Groups B and C had been used as test animals in Experiment I. The last inoculation, therefore, was actually the second reinoculation, although no evidences of syphilis developed after the first reinoculation.

The test inoculations were made intracutaneously in two different areas in each animal. Fourteen normal rabbits were similarly inocu-

TABLE I

Experiment I (see Appendix A)

Rabbit number	Sex	First infection: Method	First infection: Local lesion	First infection: General lesions	Test inoculation—intracutaneous: Treatment after first inoculation	Test inoculation—intracutaneous: Days after first inoculation	Test inoculation—intracutaneous: Allergic manifestations	Test inoculation—intracutaneous: Microscopic sections	Test inoculation—intracutaneous: Local lesion	Test inoculation—intracutaneous: General lesion	Test inoculation—intracutaneous: Duration of observation	Controls—intracutaneous inoculation: Rabbit number	Sex	Microscopic section	Local lesion	General lesions	Duration of observation
								days			*days*			*days*			
2049	F.	Intravenous	−	+ (B.S.)	None	188	0*	1	0	0	365	2321	M.	1	+	+ (T.S.E.)	345
														41			
1945	M.	Intratesticular	+	0	None	288	0	2	0	0	372	2322	M.	2	+	0	363
2013	F.	Intravenous	−	+ (B.S.)	None	188	0	3	0	0	365	2320	M.	3	+	0	276
2010	F.	Intravenous	−	+ (B.S.)	None	188	0	4	0	0	365	2324	F.	4	+	0	363
2122	M.	Intratesticular	+	0	None	188	0	5	0	0	365	2326	F.	5	+	0	276
2120	M.	Intratesticular	+	0	None	188	0	6	0	0	365	2317	M.	6	+	0	186
2052	F.	Intravenous	−	+ (S)	None	188	0	10	0	0	365	2333	F.	10	+	0	377
1975	F.	Subcutaneous	+	0	None	288	0	15	0	0	372	2325	F.	15	+	0	377
1978	F.	Subcutaneous	±	0	None	288	0	20	0	0	372	2330	F.	20	+	+ (B)	372
2051	F.	Intravenous	−	+ (B.S.)	None	188	0	28	0	0	188	2331	F.	28	+	+ (B.S.)	377
1943	M.	Intratesticular	+	+ (B)	None	288	0	41	0	0	159	2319	M.	−	+	0	363
1947	M.	Intratesticular	+	0	None	288	0	−	0	0	372	2323	M.	−	+	−	34
1976	F.	Subcutaneous	+	0	None	288	0	−	0	0	376	2327	F.	−	±	0	120
1979	F.	Subcutaneous	+	0	None	288	0	−	0	0	376	2329	F.	−	+	0	155
2121	M.	Intratesticular	+	0	None	188	0	−	0	0	240	2332	F.	−	+	+ (S)	276

T—testicular lesion; B—periosteal-bone lesions; S—skin lesion; E—eye lesion.

* By "allergic manifestations" we mean any more prominent inflammatory changes (redness, oedema, infiltration with inflammatory exudate) in the macroscopic or microscopic appearance of the lesions in the reinoculated as compared with the control animals. Limitation of space forbids a detailed description of each lesion on each successive day. See Appendix for summaries.

lated as controls. As in the previous experiment all animals were observed for any manifestation of an allergic reaction at the sites of inoculation, and for the occurrence of local or generalized syphilitic lesions. Microscopic sections from one animal of each group and from the controls were made on the first, second, third, sixth, fifteenth, twenty-sixth, thirty-fourth, and forty-fourth day after inoculation.

The pertinent details along with the results of this experiment are shown in Table II. All of the test animals were refractory to the virus, not a single one showed any evidence of an allergic reaction upon reinoculation. The day following inoculation practically every animal, control as well as test animals, showed a small erythematous papule at the site of inoculation. This reaction began to subside on the second day and had disappeared by the fifth day. Throughout this period no difference whatever could be noted between the reaction in the test and the control animals. By the tenth day all of the control animals exhibited a lesion in the inoculated area, which in another ten days had developed into a typical chancre. Three of the control animals subsequently developed generalized lesions. No test animal developed a macroscopic syphilitic lesion during the period of observation. A description of the microscopic sections of the excised inoculated areas is given in Appendix B.

From this experiment, it is again clear that reinoculation with an homologous strain after the first infection has reached a period of latency gives rise to no allergic reaction whatever, although the animals are immune.

Expt. III. This experiment was devised to determine whether rabbits reinoculated with an homologous strain of syphilis at a time when there are progressing lesions as a result of a first infection show an allergic reaction at the site of a second inoculation. It was expected, on the basis of the work of others, that these animals would not be so highly immune to a second inoculation. Ten male rabbits were inoculated intracutaneously and twenty-eight days later, at a time when each exhibited a progressing chancre, reinoculation with an homologous virus was performed. A like number of normal rabbits were similarly inoculated as controls. In no instance was there any evidence of an allergic reaction in the test animals. It will be observed in Table III that at the time of the second inoculation not all

TABLE II

Experiment II (see Appendix B)

GROUP	RABBIT NUMBER	SEX	FIRST INFECTION				TEST INOCULATION—INTRACUTANEOUS						CONTROLS—INTRACUTANEOUS INOCULATION					
			Method	Local lesion	General lesions	Treatment—days after first inoculation	Days after first inoculation	Allergic manifestations	Microscopic section	Local lesion	General lesion	Duration of observation	Rabbit number	Sex	Microscopic section	Local lesion	General lesions	Duration of observation
									days			*days*			*days*			*days*
A	1880	M.	Subcutaneous	+	0	187*	482	0	1	0	0	240	2437	M.	1	+	0	261
	1878	M.	Subcutaneous	+	+ (TBS)	187*	482	0	2	0	0	54	2442	M.	2	+	0	261
	1879	M.	Subcutaneous	+	+ (T)	187*	482	0	3	0	0	108	2444	M.	3	+	0	261
	1887	M.	Subcutaneous	+	+ (E)	187*	482	0	6	0	0	116	2438	M.	6	+	−	33
	1918	M.	Intravenous	−	+ (TBE)	187*	482	0	15	0	0	240	2427	M.	15	+	0	113
	1919	M.	Intravenous	−	+ (TBS)	187*	482	0	26	0	0	83	2447	M.	26	+	+ (B)	61
	1865	M.	Wound	+	+ (BE)	187*	482	0	34	0	−	40	2443	M.	34	+	+ (TE)	90
	1904	M.	Subcutaneous	+	0	187*	482	0	−	−	−	7	2439	M.	44	+	0	261
B	1945	M.	Intratesticular	+	+ (B)	None	415	0	1	0	0	246	2433	M.	−	+	0	89
	1947	M.	Intratesticular	+	0	None	415	0	2	0	0	246	2440	M.	−	−	−	10
	1975	F.	Subcutaneous	+	0	None	415	0	3	0	0	246	2445	M.	−	+	+ (T)	261
	1978	F.	Subcutaneous	+	0	None	415	0	6	0	0	246	2446	M.	−	+	−	25
	1976	F.	Subcutaneous	+	0	None	415	0	15	0	0	250	2450	M.	−	+	0	261
	1979	F.	Subcutaneous	+	0	None	415	0	26	0	0	250	2451	M.	−	+	0	261
C	2051	F.	Intravenous	−	+ (BS)	None	314	0	1	0	0	62						
	2120	M.	Intratesticular	+	0	None	314	0	2	0	0	238						
	2049	F.	Intravenous	−	+ (BS)	None	314	0	3	0	0	240						
	2121	M.	Intratesticular	+	0	None	314	0	6	0	0	110						
	2122	M.	Intratesticular	+	0	None	314	0	15	0	0	239						
	2010	F.	Intravenous	−	+ (BS)	None	314	0	26	0	0	239						
	2013	F.	Intravenous	−	+ (BS)	None	314	0	34	0	0	239						
	2052	F.	Intravenous	−	+ (S)	None	314	0	44	0	0	239						

D	2330	F.	Intracutaneous	+	+ (B)	None	128	0	1	0	0	244						
	2321	M.	Intracutaneous	+	+ (TSE)	None	128	0	2	0	0	214						
	2324	F.	Intracutaneous	+	0	None	128	0	3	0	0	239						
	2320	M.	Intracutaneous	+	0	None	128	0	6	0	0	160						
	2326	F.	Intracutaneous	+	0	None	128	0	15	0	0	250						
	2319	M.	Intracutaneous	+	0	None	128	0	26	0	0	238						
	2317	M.	Intracutaneous	+	0	None	128	0	34	0	–	40						
	2331	F.	Intracutaneous	+	+ (BS)	None	128	0	44	0	0	251						
	2322	M.	Intracutaneous	+	0	None	128	0	–	0	0	238						
	2325	F.	Intracutaneous	+	0	None	128	0	–	0	0	251						
	2329	F.	Intracutaneous	+	0	None	128	0	–	0	–	28						
	2332	F.	Intracutaneous	+	+ (S)	None	128	0	–	0	0	250						
	2333	F.	Intracutaneous	+	0	None	128	0	–	0	0	250						

* Six arsphenamine treatments, each 20 mgm. per kgm.

of the test animals had developed a high degree of immunity. Four of the ten test animals developed chancres as a result of the second inoculation, but even in these animals some resistance to infection was present, for in the case of each animal which developed a local lesion from the second inoculation, the incubation period of these lesions was longer than that in the controls and, moreover, the lesions in the test animals never attained the size of those in the controls. In two of the test animals (2442 and 2443, Table III) a tiny papule appeared at the site several weeks after the second inoculation and in each case disappeared after one week, the site remaining normal thereafter. It is impossible to be sure of the nature of these papules. They may have been delayed and abortive chancres. Microscopic sections of areas removed on the first, second, sixth and sixteenth days showed no allergic reaction whatever as compared with the sections of the controls. A description of these sections is given in Appendix C.

From this experiment it can be said that rabbits, in this early stage of a primary infection before immunity is well developed, show no allergic reaction upon reinoculation. It may be mentioned that Uhlenhuth and Mulzer (10), without entering into experimental details, state that they were never able to produce an allergic reaction by rubbing spirochaetes into scarified areas or by injecting them into the skin of rabbits in the early stage of syphilitic infection. They do not state whether they made any attempts to elicit allergic reactions during the later stages of the infection.

Expt. IV. The object of this experiment was mainly to repeat certain aspects of Experiments I and II. In this series, however, each animal was inoculated in six different areas on the back, and a site of inoculation was removed from the same animal on the first, third, sixth, and tenth day after inoculation. This afforded an opportunity to observe the microscopic reaction in the same animal at four different periods after inoculation.

Four test animals were infected first by intracutaneous inoculation, treated with arsphenamine as described above approximately six months later, and reinoculated 370 days after the first inoculation. It will be noted that these same rabbits were among the test animals in Experiment III, therefore the inoculation for Experiment IV repre-

TABLE III

Experiment III (see Appendix C)

RABBIT NUMBER	SEX	FIRST INFECTION				TEST INOCULATION, INTRACUTANEOUS—28 DAYS AFTER FIRST INOCULATION					CONTROLS—INTRACUTANEOUS INOCULATION					
		Method	Local lesion	General lesions*	Treatment after first inoculation	Syphilitic lesion present at time of test inoculation	Allergic manifestations	Microscopic section	Local lesion	Duration of observation	Rabbit number	Sex	Microscopic section	Local lesion	General lesion	Duration of observation
								days		*days*			*days*			*days*
2427	M.	Intracutaneous	+	0	None	+	0	1	0	85	2435	M.	1	+	0	223
2437	M.	Intracutaneous	+	0	None	+	0	2	+	261	2453	M.	2	+	0	223
2443	M.	Intracutaneous	+	+ (TE)	None	+	0	6	?†	203	2456	M.	6	+	0	223
2439	M.	Intracutaneous	+	0	None	+	0	16	0	203	2452	M.	16	+	+ (S)	55
2450	M.	Intracutaneous	+	0	None	+	0	16	+	203	2455	M.	−	+	0	60
2433	M.	Intracutaneous	+	0	None	+	0	−	+	61	2457	M.	−	+	0	223
2442	M.	Intracutaneous	+	0	None	+	0	−	?†	203	2458	M.	−	+	−	20
2444	M.	Intracutaneous	+	0	None	+	0	−	0	203	2459	M.	−	+	0	223
2445	M.	Intracutaneous	+	+ (T)	None	+	0	−	0	203	2460	M.	−	+	0	223
2447	M.	Intracutaneous	+	+ (B)	None	+	0	−	+	203	2461	M.	−	+	+ (TBS)	223

* Because of the short interval between the first and test inoculation where general lesions occurred it was impossible to determine to which inoculation these lesions were due. It may be assumed that they were produced by the first inoculation.

† See text for description of this lesion.

TABLE IV

Experiment IV (see Appendix D)

RABBIT NUMBER	SEX	FIRST INFECTION				TEST INOCULATION, INTRACUTANEOUS—6 AREAS						CONTROLS—INTRACUTANEOUS INOCULATION, 6 AREAS					
		Method	Local lesion	General lesion	Treatment—days after first inoculation	Days after first inoculation	Allergic manifestations	Microscopic section	Local lesion	General lesion	Duration of observation	Rabbit number	Sex	Microscopic section	Local lesion	General lesions	Duration of observation
								days						*days*			
2444	M.	Intracutaneous	+	0	203*	370	0	1 3 6 10	0	0	83	2885	M.	1 3 6 10	+	0	83
2450	M.	Intracutaneous	+	0	203	370	0	1 3 6 10	0	0	43	2886	M.	6	+	+ (BS)	83
2439	M.	Intracutaneous	+	0	203	370	0	6	0	0	83						
2447	M.	Intracutaneous	+	+ (B)	203	370	0	–	0	0	83						

* Six arsphenamine treatments, each 20 mgm. per kgm.

sented actually the second reinoculation of these animals, although antisyphilitic treatment had been given in the meantime. Following the test inoculation no allergic reaction was noted in any of the animals. No syphilitic lesions developed in the test animals during the period of observation. In the two control animals small syphilitic lesions were noted on the sixth day and by the tenth day these were quite definite chancres.

This experiment affords additional evidence that rabbits infected with syphilis, treated late in the course of the disease and shown to be immune, exhibit no allergic reaction upon reinoculation. In addition to macroscopic observation, microscopic study of inoculated areas of the same animal on several occasions within the first ten days revealed no trace of an allergic reaction. A description of the microscopic sections is given in Appendix D.

DISCUSSION

By far the greater part of the work done on the relation of allergy to immunity has been carried out in tuberculosis, with the guinea pig as the experimental animal. It is quite true that, in tuberculosis in the guinea-pig, allergy and immunity ordinarily develop together. From this circumstance, and from various speculative considerations, it has been concluded that the allergic inflammatory reaction is essential for immunity. This conclusion was then widely transferred to bacterial diseases in general (we have quoted above examples of its application to syphilis) in spite of the fact that there is no experiment on record in which allergy has been shown to be necessary for immunity under any condition in any infection. Several years ago one of us drew attention to numerous reasons for questioning the supposed necessity of allergy for the operation of acquired immunity (5) (6). Since then it has been possible to demonstrate that in pneumococcal infection immunity can be completely dissociated from allergy by the method of passive immunization (7), and also that immunity can be separated from allergic inflammation in pneumococcal and pasteurella infection by abolishing the hypersensitiveness of an immune allergic animal through desensitization (8). In both of the latter studies immunity remained intact in the complete absence of allergic inflammation. In still further studies it was shown that the local

immobilization of bacteria in the immune body, a manifestation of immunity which has been generally supposed to be the effect of allergic inflammation, is completely independent of hypersensitiveness and is caused primarily by a totally different mechanism (6). Even in tuberculosis, the prime infection in which allergy and immunity have long been regarded as inseparable, the separation by the method of desensitization has recently been accomplished with complete success by Rothschild, Bernstein and Friedenwald in the Pathological Department of this University (9).

To these demonstrations that allergy is not necessary for the operation of immunity, the present experiments on syphilis add still further evidence from a different angle. The experiments reported here show that, without recourse to such procedures as desensitization, active immunity can be established and can operate efficiently in the complete absence of allergic inflammation, and this in an infection which resembles tuberculosis in so many ways, clinically and pathologically, that many writers have drawn a close parallel between the pathogenesis of the two diseases. Furthermore, this work was done on an infection in which allergy is well known to appear in human beings, and in which immunity has been claimed to be absolutely dependent upon allergy, as we have pointed out above. It may be remarked that the use of the rabbit as the experimental animal, and the skin as the site of infection, is free from any objection regarding the susceptibility of animal or site to syphilitic allergic reactions, for it was in the skin of the rabbit that Noguchi first demonstrated the presence of allergy in syphilis (1). In a number of our experiments the test infection has been made intratesticularly as well as intracutaneously. Serial sections would be necessary in order to be certain of the total extent of the lesions in the testes, and these were not made; but in the sections which were made through the sites of infection there was never any suggestion of an allergic reaction in the immune animals.

These experiments do not, of course, dispose of the possibility of rabbits ever becoming allergic during the course of infection with syphilis, but it has never been shown by anyone, so far as we are aware, that they do. The rabbits in which Noguchi produced the allergic state were sensitized by repeated intravenous injections of emulsions of syphilitic testes of rabbits. The experiments are not given in detail,

and there is no mention as to whether those particular rabbits ever developed any manifestation of syphilitic infection. In other rabbits with an active syphilitic orchitis the cutaneous reactions obtained by Noguchi were regarded by him as doubtful, even though the test emulsion used by him contained far more spirochaetes than that used in the present experiments. We are inclined to be doubtful that rabbits would ever show allergic reactions to *Treponema pallidum* during the course of experimental syphilitic infection when the antigen used in testing for the presence of the allergic state is an emulsion of a syphilitic rabbit testis containing living spirochaetes, such as we have used; and yet, in the complete absence of allergic inflammation, immunity was effective, although the test dose always contained far more virulent spirochaetes than could ever conceivably be suddenly deposited in the tissues at one spot in natural infection.

SUMMARY

Rabbits rendered immune to syphilis by inoculation with *Treponema pallidum* showed no allergic reaction whatever, whether macroscopically or microscopically, on intracutaneous reinoculation at periods ranging from 28 days to 482 days after the primary, immunizing infection. On the contrary, the most striking phenomenon observed in the immune animals, as contrasted with the non-immune controls, was always a remarkable indifference of the tissues of the former to the presence of the injected virus. Although allergy to *Treponema pallidum* is well known to appear during human syphilitic infection, and can also be induced in the rabbit, according to Noguchi, the present experiments demonstrate that allergic inflammation is not necessary for the operation of acquired immunity in syphilis.

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APPENDIX A

Microscopical study of sites of test infection in Experiment I (see Table I)

24 hours: Immune (2049) and control (2321) both show mild acute inflammation. No difference in intensity or degree between the two.

2 days: Immune (1945)—Slight residue of acute inflammation. Small accumulations of mononuclear cells about two blood vessels.
Control (2322)—Slight residue of acute inflammation. Mononuclear cells about numerous blood vessels.

3 days: Immune (2013)—Few mononuclear cells about several blood vessels.
Control (2320)—Residue of acute inflammation still present; also mononuclear cells about vessels and occasional hair follicles.

4 days: Immune (2010)—Clumps of mononuclear cells about a few vessels and hair follicles.
Control (2324)—Mononuclear cells about hair follicles and small blood vessels.

5 days: Immune (2122)—Practically no trace of inflammation.
Control (2326)—Infiltration of mononuclear and occasional polymorphonuclear cells about numerous blood vessels and hair follicles.

6 days: Immune (2120)—One section shows small accumulation of mononuclear cells about a blood vessel. The other sections are normal.
Control (2317)—There is a definite, developing chancre.

10 days: Immune (2052)—A few minute accumulations of mononuclear cells about blood vessels.
Control (2333)—Abundant accumulations of mononuclear cells about blood vessels and hair follicles, with very few polymorphonuclear cells—a definite, developing chancre.

15 days: Immune (1975)—Occasional minute groups of mononuclear cells about hair follicles.
Control (2325)—Well developed chancre, with replacement of tissue by masses of mononuclear cells (epithelioid cells, lymphocytes).

20 days: Immune (1978)—Several minute accumulations of mononuclear cells.
Control (2330)—Well developed chancre.

28 days: Immune (2051)—One section shows a small area in which there are mononuclear cells with numerous polymorphonuclear cells just beneath the epithelium at a place where there is a small break in the epithelium covered by a scab. This appears to be the result of a scratch. There is no localization of the inflammatory cells about blood vessels or hair follicles in the manner characteristic of syphilis. The remaining sections are normal.
Control (2331)—Well developed chancre.

41 days: Immune (1943)—Normal skin.
Control (2321)—Large chancre with ulceration and with destruction of corium almost down to underlying muscle.

APPENDIX B

Microscopic study of sites of test infection in experiment II (see Table II)

24 hours: Immune, Series A (1880), B (1945), C (2051) and D (2330). All show acute inflammation in corium but in each case the inflammation is distinctly *less* than in the control.
Control (2437)—Mild acute inflammation in corium.

2 days: Immune, Series A (1878)—Inflammation of same degree as in control.
Immune, Series B (1947)—Less inflammation than in control.
Immune, Series C (2120)—Less inflammation than in control.
Immune, Series D (2321)—Same amount of inflammation as in control.
Control (2442)—Subsiding inflammation. Less than at 24 hours (2437).

3 days: Immune, Series A (1879), B (1975), C (2049) and D (2324)—Very few inflammatory cells left at site. Some show less, none more inflammation than control.
Control (2444)—Few inflammatory cells in corium. Subsiding inflammation.

6 days: Immune, Series A (1887)—Practically normal. Occasional mononuclear cells beneath epithelium.
Immune, Series B (1978)—Few mononuclear cells about healing needle puncture. Far less inflammation than in control.
Immune, Series C (2121)—Small accumulations of mononuclear cells about two blood vessels. Far less inflammation than in control.
Immune, Series D (2320)—No accumulations of mononuclear cells seen. Normal except for healing needle puncture.
Control (2438)—Definite beginning syphilitic lesion, characterized by infiltration of mononuclear cells about blood vessels of corium and about hair follicles.

15 days: Immune, Series A (1918)—Immediately beneath the epithelium in several places there are a very few polymorphonuclear leucocytes. No mononuclear cells about blood vessels or hair follicles.
Immune, Series B (1976)—Several mononuclear cells about a blood vessel in one place in the corium.
Immune, Series C (2122)—Normal skin.
Immune, Series D (2326)—Several minute clumps of mononuclear cells immediately beneath the epithelium, and one small clump near a blood vessel in the corium.
Control (2427)—Well developed chancre, with abundant infiltration of mononuclear cells about blood vessels and hair follicles and with destruction of corium and base of hair follicles.

26 days: Immune, Series A (1919)—Perfectly normal skin.
Immune, Series B (1979)—Small clumps of mononuclear cells about blood vessels and hair follicles. The lesion is characteristic of syphilis and is about the extent shown by non-immune controls after a lapse of four days, whereas this lesion is four weeks old.
Immune, Series C (2010)—Normal except for an occasional polymorphonuclear leucocyte immediately beneath epithelium.
Immune, Series D (2319)—Occasional groups of two or three mononuclear cells immediately beneath epithelium. No cells about blood vessels or hair follicles.
Control (2447)—Well developed chancre with ulceration.
34 days: Immune, Series A (1865)—Definite but slight mononuclear cell infiltration about several hair follicles.
Immune, Series B—No sections. There were only 6 animals in this group and the lesion in each has already been removed and described.
Immune, Series C (2013)—Normal, except for occasional mononuclear cells immediately beneath epithelium.
Immune, Series D (2317)—Perfectly normal skin.
Control (2443)—Large ulcerated chancre.
44 days: Immune, Series A and B—No sections.
Immune, Series C (2052)—Perfectly normal skin.
Immune, Series D (2331)—Slight but definite mononuclear infiltration about a few hair follicles and blood vessels.
Control (2439)—Huge ulcerated chancre, secondarily infected.

APPENDIX C

Microscopic study of sites of test infection in Experiment III (see Table III)

24 hours: Immune (2427)—Mild acute inflammation, less than in control.
Control (2435)—Mild acute inflammation of corium.
2 days: Immune (2437)—Inflammation of same degree as in control.
Control (2453)—Slight residual inflammation.
6 days: Immune (2443)—Slight mononuclear cell infiltration about hair follicles and blood vessels, about same as in control.
Control (2456)—Slight mononuclear cell infiltration about hair follicles and blood vessels.
16 days: Immune (2439)—One minute accumulation of mononuclear cells about a hair follicle.
Immune (2450)—Small accumulations of mononuclear cells about numerous hair follicles.
Control (2452)—Well developed chancre.

APPENDIX D

Microscopic study of sites of test infection in Experiment IV (see Table IV)

24 hours: Immune (2444)—Inflammation of same degree as in control.
Immune (2450)—Inflammation of same degree as in control.
Control (2885)—Acute inflammation of corium.

3 days: Immune (2444)—There is what appears to be a piece of injected dead tissue surrounded by mononuclear cells in one section; otherwise practically normal.
Immune (2450)— Practically normal. Very slight residue of inflammation.
Control (2885)—Practically normal. Very slight residue of inflammation.

6 days: Immune (2444)—Small clumps of mononuclear cells about blood vessels at area of healing needle puncture. Far less than in control.
Immune (2450)—Occasional groups of mononuclear cells about blood vessels. Far less than in control.
Immune (2439)—Several minute accumulations of mononuclear cells about blood vessels.
Control (2885)—Much mononuclear infiltration about blood vessels and hair follicles.
Control (2886)—Pronounced mononuclear infiltration about blood vessels and hair follicles.

10 days: Immune (2444)—Occasional minute clumps of mononuclear cells about blood vessels.
Immune (2450)—Mononuclear infiltration about blood vessels and hair follicles, but much less than in control.
Control (2885)—Well developed chancre.

EXPLANATION OF ILLUSTRATIONS

The photographs are from animals in Experiment I and in each case were selected to show the sites of greatest reaction. (Photographs by Mr. Milton Kougl.)

FIGS. 1 AND 2

Figure 1 (control rabbit 2321) and figure 2 (immune rabbit 2049) show the sites of infection 24 hours after the test injection. There is no more inflammation in the immune animal than in the normal.

FIGS. 3 AND 4

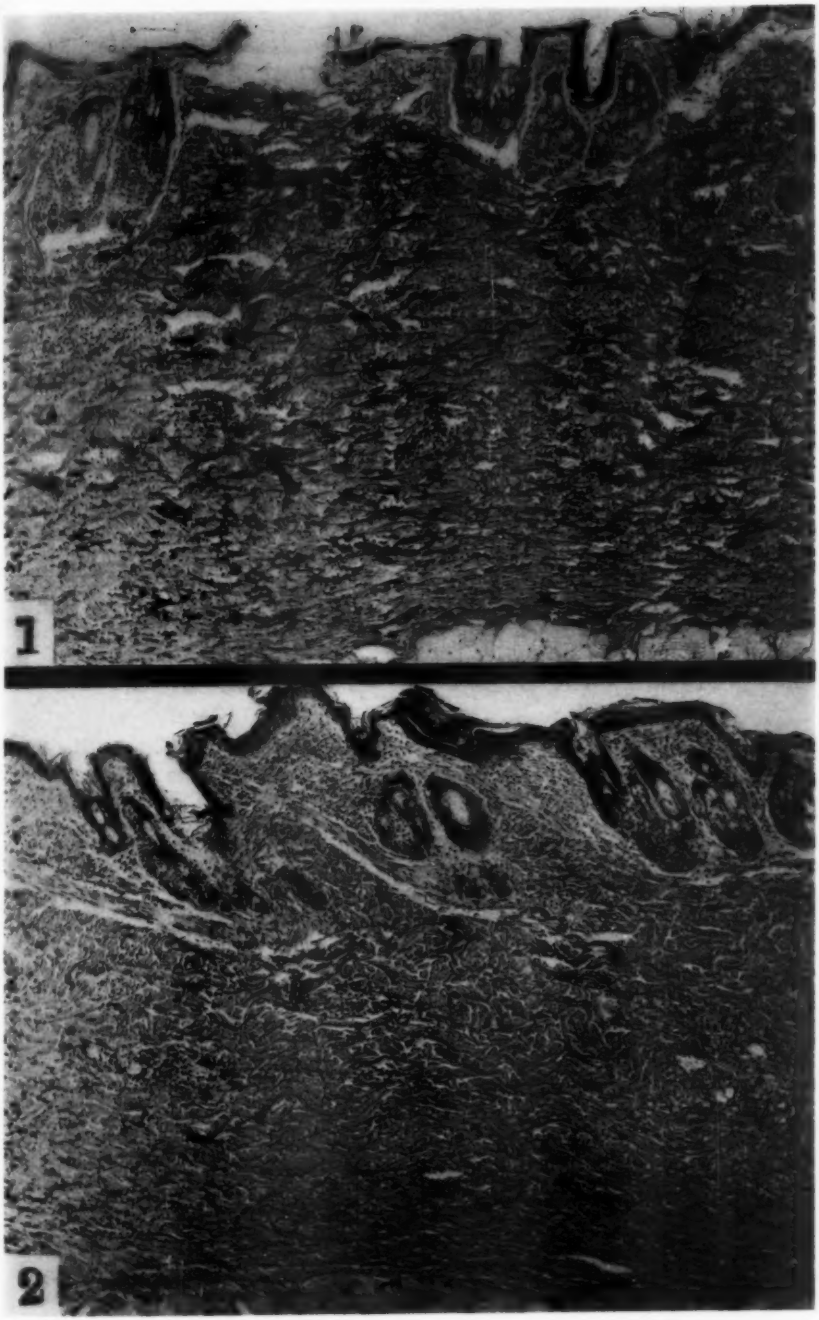
Figure 3 (control rabbit 2322) and figure 4 (immune rabbit 1945) show the sites of infection 48 hours after the test injection. In the sections there is more inflammation in the control than in the immune animal rather than the reverse. Obviously, therefore, there is no allergic reaction in the immune.

FIGS. 5 AND 6

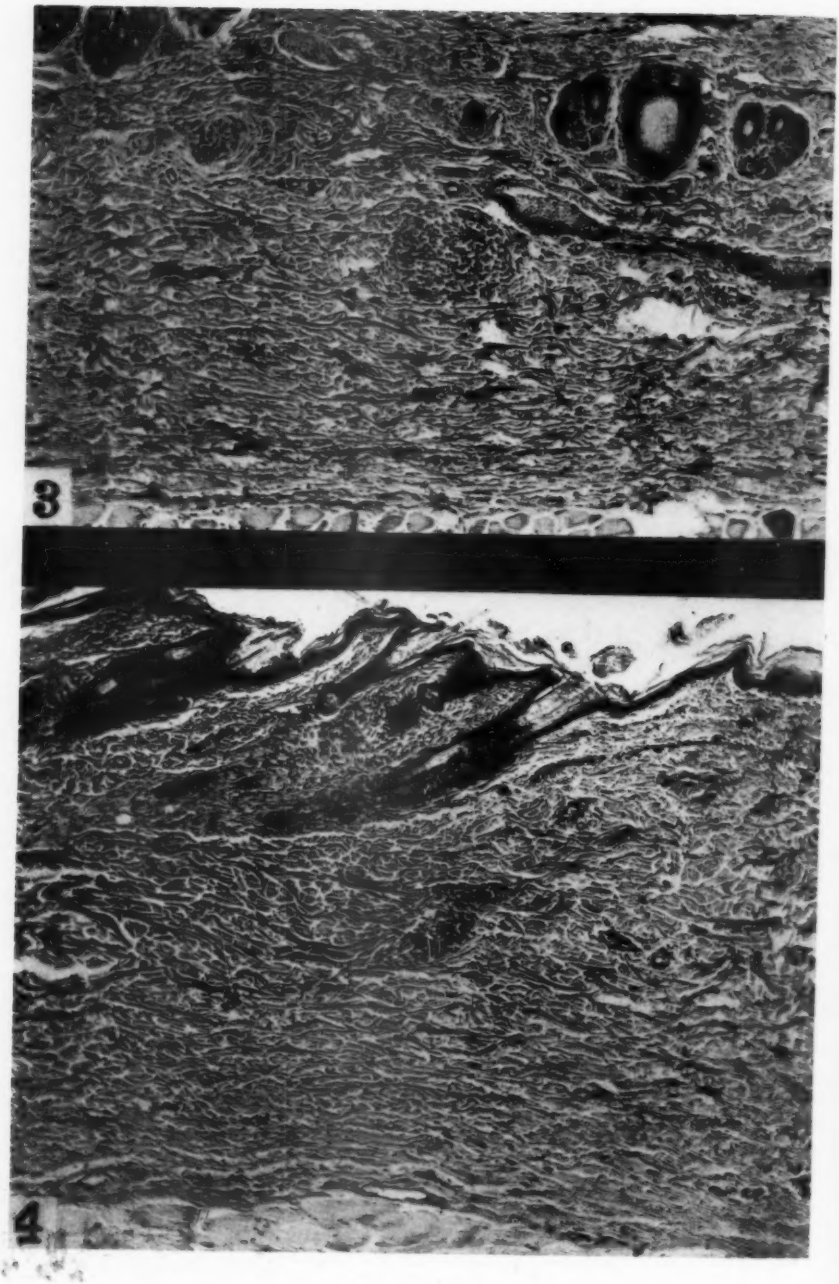
Figure 5 (immune rabbit 1975) and figure 6 (control rabbit 2325) show the sites of infection after 15 days. The immune animal shows only a few mononuclear cells about several hair follicles, whereas the control shows a well developed chancre with destruction of the corium.

FIGS. 7 AND 8

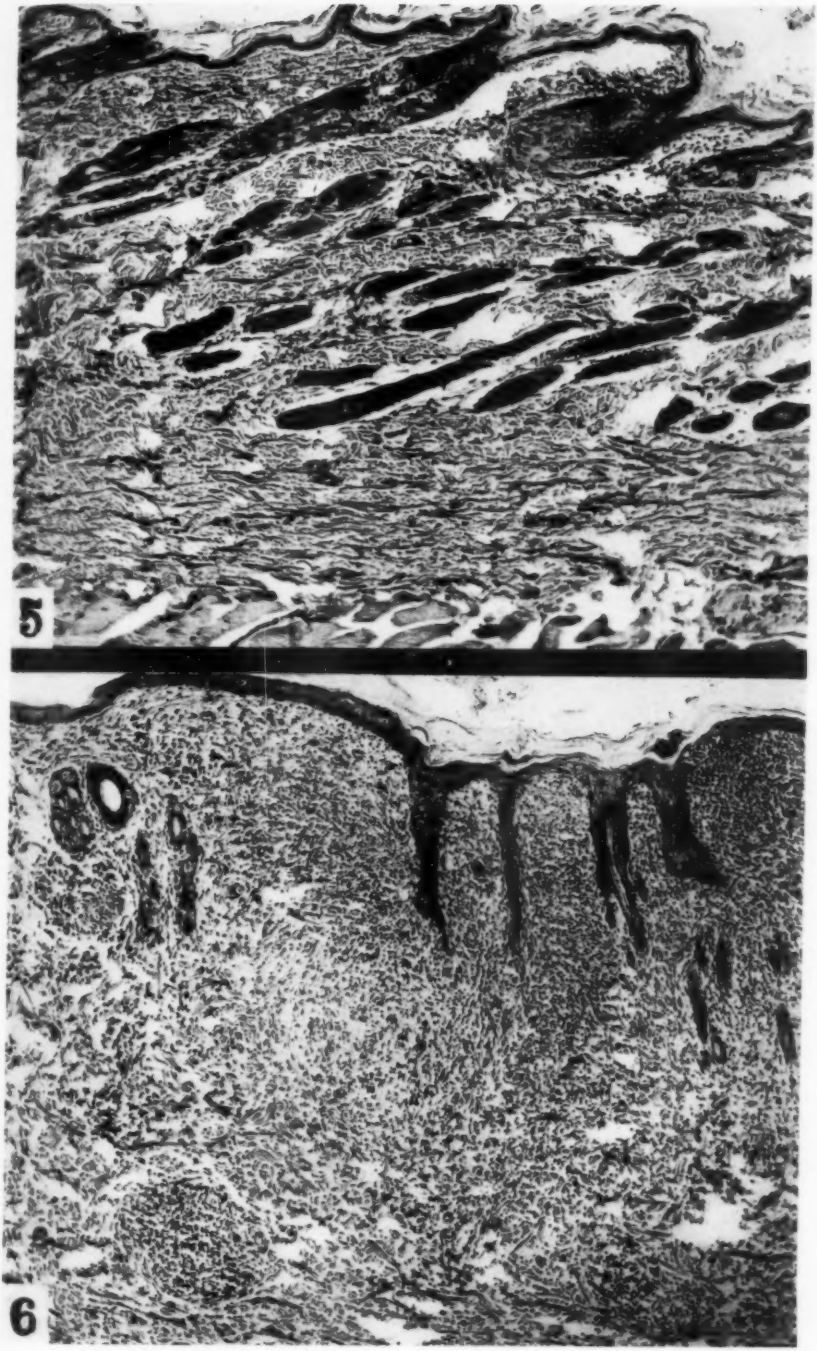
Figure 7 (control rabbit 2330) and figure 8 (immune rabbit 1978) show the sites of infection (centers of the inked circles) 20 days after infection. The skin of the immune animal is perfectly normal macroscopically, and microscopically shows only several minute groups of mononuclear cells. The control shows a well-developed chancre with beginning ulceration.



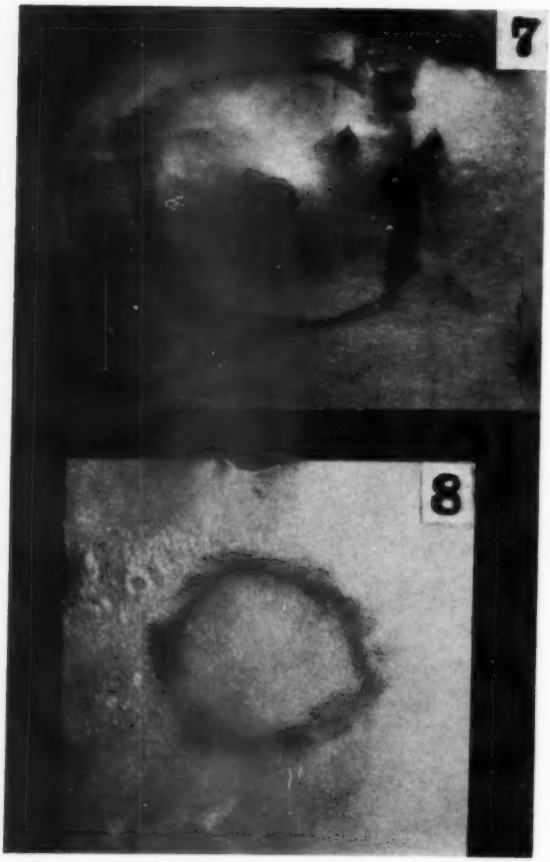
FIGS. 1 AND 2



FIGS. 3 AND 4



FIGS. 5 AND 6



FIGS. 7 AND 8

THE MECHANISM RESPONSIBLE FOR THE PREVENTION OF SPREAD OF BACTERIA IN THE IMMUNE BODY[1]

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It has been known for many years that when bacteria are deposited in the tissues of the immune body the danger of septicaemia and of metastasis of infection to distant tissues is far less than in the non-immune body. In pneumococcal infection, for example, Wadsworth (1) found that virulent pneumococci placed in the lungs of susceptible animals ordinarily invaded the blood stream so rapidly that the animals died from septicaemia before a well developed lobar pneumonia appeared. In contrast, when they were placed in the lungs of immunized animals septicaemia was inhibited, the infection tended to remain localized in the lungs and the animals ordinarily survived. In tuberculous infection Willis, in a careful series of studies, found that bacilli deposited in the skin of the normal body have already spread from the site at the end of an hour (Kagayama found them in the regional nodes five minutes after placing them in the peritoneal cavity (3)), whereas in the immune guinea-pig the spread of bacilli from the site of inoculation is greatly inhibited (2). It would be superfluous to enumerate further examples of the local immobilization of bacteria in the immune body. The phenomenon is thoroughly familiar in every disease caused by bacteria which tend to produce metastatic foci of infection, and its importance as a protective process is too obvious to require comment. The intimate nature of the mechanism responsible for the immobilization of the bacteria has, however, been a matter of question. Those who have previously investigated the problem have concluded that the bacteria are held fixed where they lodge by the mechanical effects of the inflammation which appears about them (4) (5) (6). Since the immune body is also frequently hypersensitive to the products of the infecting bacteria, the tissues are more rapidly and

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more severely damaged wherever the bacteria lodge, and inflammation is consequently accelerated and exaggerated at the site. This more prompt allergic inflammation has therefore been widely regarded as the means by which the bacteria are mechanically hemmed in at the site where they lodge in the immune body.

The view that it is inflammation which is primarily responsible for the local immobilization of bacteria in the immune body is based entirely upon two facts. First, in localized lesions bacteria are commonly found surrounded by a wall of inflammatory exudate and, in addition, when the inflammation is severe, small veins and lymphatics draining the area may be occluded by thrombi. Unquestionably, *once they are formed* the wall of leucocytes and fibrin and the thrombi obstructing the drainage do inhibit the free drift of bacteria from the site, but this morphological observation leaves quite unanswered the question as to why the bacteria remained localized at the site long enough to be so competently encapsulated. The second fact upon which is built the belief that the inhibition of spread of bacteria is simply a mechanical result of inflammation is the old experimental observation that if an area of non-specific inflammation be established by the application of an irritant and bacteria be then deposited in the inflamed area, the spread of the bacteria will be inhibited. This fact, which was pointed out some forty years ago by Cobbett and Melsome (8) and others, and which has recently been revived, unquestionably proves that *once it is formed* an area of inflammation tends to prevent the spread of bacteria deposited in it. However, as has been discussed at length in another place (7), there are numerous and weighty objections which render this type of experiment totally inadequate to serve as proof of the conclusion drawn from it—*i.e.*, the conclusion that the spread of bacteria in the immune body is inhibited primarily by the process of inflammation. Chief among these objections is the fact that in natural infection the site at which bacteria lodge in the tissues is not an area of previously established inflammation but a normal area, and the inflammation appears *after*, not *before*, the bacteria lodge there. This circumstance is a very important one, for it happens that if an irritant, which produces an inflammatory reaction capable of inhibiting the spread of bacteria subsequently deposited there, be injected into normal tissues together

with the bacteria so that an accelerated inflammation begins just *after* the bacteria reach the tissues, as is the case in natural infection in general and in allergic reactions in particular, the spread of the bacteria is never inhibited and is often actually accelerated (7) (8).

Indeed, since it is well known that bacteria begin to drift immediately from the site where they lodge in the non-immune body, it becomes entirely unlikely that in the immune body an amount of inflammation sufficient to wall them in mechanically could appear rapidly enough to stop their immediate drift from the site. Certainly, as far as macroscopic observation permits one to judge, not even the accelerated inflammation of allergy appears quickly enough to accomplish that effect. We need only recall as an example the fact that tubercle bacilli have been shown to spread from the site of inoculation within a matter of minutes after having been deposited in the normal body, whereas hours elapse before any trace of inflammation becomes visible macroscopically at the site even in the allergic, immune body in which the movement of the bacilli is inhibited. However, since those who ascribe the prevention of the immediate spread of bacteria to inflammation universally assume that an effective amount of inflammation does appear rapidly enough to prevent that spread, the present experiments, of which a brief abstract has already been published (9), were undertaken with the object of studying microscopically the course of events at the site of infection in the immune body. As far as I have been able to find, no one has previously attempted to follow from this standpoint the course of infection and the movement and fate of the bacteria in the tissues of the immune as compared with those of the non-immune body. Several years ago a thorough analysis of the question of local fixation of bacteria led to the conclusion that the process must be governed primarily by the specific effect of antibody (19) (7). The present experiments afford additional and direct evidence of the correctness of that view.

EXPERIMENTS

Type I pneumococcal infection of the skin of the rabbit was chosen for the purposes of this study for the following reasons: In the non-immune rabbit the infection runs its course to a fatal termination within 24 to 36 hours; the bacteria spread rapidly from the site where

they are placed, with the result that a progressively spreading local lesion develops and septicaemia is well established after a few hours; a high degree of allergy and of immunity can be established by vaccination with dead organisms; in the immunized animal the bacteria are held at the site of infection, the lesion remains localized, septicaemia does not occur and the animal survives; we have shown (10) that immunity in this infection can be completely separated from allergic inflammation; and finally, the pneumococcus can be stained very readily in sections and the movement and fate of those injected can thus be followed microscopically with great ease. The skin was chosen as the site of infection for the reason that cutaneous lesions can be kept continually under macroscopic observation during the entire experiment and can easily be removed for microscopical study at any desired intervals.

The local immobilization of pneumococci in the immune, allergic body. In the first series of experiments rabbits were rendered immune by repeated intravenous injections of heat-killed Type I pneumococci. The organisms were either washed from blood-agar plates, or else broth cultures were centrifugalized and washed in normal saline. They were killed by heating in a water-bath for one hour at 60°C. One cubic centimeter of a heavy suspension of dead organisms was injected into the ear vein every fifth day. At the end of six weeks the intravenous injections were discontinued and the animals were given a series of intracutaneous injections of 0.1 c.c. of a concentrated suspension of killed pneumococci at five-day intervals, until a high degree of hypersensitiveness was manifested by the appearance of marked allergic reactions at the sites where the vaccine had been injected. Intravenous vaccination, although it establishes a superb degree of immunity, ordinarily leaves a lower degree of allergy than does intracutaneous vaccination. Indeed, some animals rendered highly immune by intravenous vaccination exhibit hardly any hypersensitiveness at all. It may be that the intravenous injections repeated at short intervals serve to reduce, by desensitization, any hypersensitiveness which may tend to develop. We have shown in another communication that hypersensitiveness to the products of the pneumococcus can be greatly reduced and even abolished by the intravenous injection of killed organisms (11), but how long this desensitization persists we have not sought to determine.

When the animals had become allergic and immune they, together with non-immune controls, were infected intracutaneously with a virulent culture of Type I pneumococcus. The cultures, grown in blood-broth, were from eight to eighteen hours old, and the dilutions used in various experiments were straight culture, 1 to 5, and 1 to 10. Animals with white skins were used and the injections in the immunized animals were always made on the side opposite to that which had been used for the intracutaneous vaccination. The hair having been removed by a non-irritating depilatory, one-tenth of a cubic centimeter of the living culture was usually injected intracutaneously at each of two widely separated sites in both the immunized and the control animals, so that one site of infection could be removed for microscopical study at any desired period and the other left as a test of immunity. In each experiment six to twelve immune animals and a corresponding number of controls were infected, so that lesions could be obtained for study at various intervals. Blood cultures were made at frequent intervals throughout the experiments.

Sites of infection were removed at intervals ranging between five minutes and twenty-four hours after the test injection. At each interval a site was removed from an immunized and also from a control animal. The various experiments provided abundant material for study taken at periods of 5 minutes, 30 minutes, 1, 2, 3, 5, 7, 9, 12, 18 and 24 hours after infection. The point at which the needle penetrated the skin was always carefully marked with ink. When the site of infection was removed for study, an area of skin and subcutaneous tissue about 2 x $1\frac{1}{4}$ inches was taken, the ink dot lying in the centre of the area. After fixation in Zenker-formol the skin was cut in thin strips for sectioning in such a way that the immediate site at which the bacteria had been deposited could be thoroughly sectioned and adjacent strips on either side as well. In addition to the block of skin taken at the site of infection, strips were often removed to a distance of four inches from the site in order to search for drifting pneumococci. The sections were stained with haematoxylin and eosin, and extra sections of each block were also stained for bacteria with MacCallum's stain, Kindell's modification of eosin methylene blue, or the bacterial stain of Brown and Brenn. Fibrin stains were made where indicated.

Macroscopically, several hours after the injection of the bacteria an elevated, pink lesion several centimeters in diameter appears at the site in the immune, allergic animals. At this time little can be seen on inspection of the site in the non-immune controls. The lesion in the allergic animals becomes more and more elevated and more pink in color, until at the end of about seven hours it appears as a sharply outlined, raised area of rather angry appearance. At this time, ordinarily, a slightly oedematous, pale lesion is visible in the non-immune controls. With the passing of time the lesion in the non-immunes becomes progressively larger, spreading downwards until it finally covers an area from the top of the back to the under surface of the abdomen. It is never as oedematous and elevated as is the lesion in the immune allergic animal except where it extends to the under surface of the abdomen where a considerable amount of inflammatory oedema tends to collect. At the end of 18 to 24 hours purpuric haemorrhages begin to make their appearance in the lesion, and before the animal dies the entire lesion may be uniformly purple from confluent haemorrhages. In contrast with the progressively spreading lesion in the non-immune animal, the lesion in the immune animal remains sharply localized, far smaller in size, and haemorrhages practically never appear. Blood cultures from the control animals become positive about 5 hours after infection, and the number of bacteria in the blood stream increases progressively thereafter until death. The blood cultures from the immunized animals, on the other hand, remain sterile throughout the experiment.

From the blood cultures and from macroscopic observation of the lesions it is perfectly obvious that the bacteria spread readily through the tissues of the non-immune animals and invade the blood stream, whereas in the immune animal their spread is prevented by some means. What is the mechanism by which this prevention of spread is accomplished? Is it merely the mechanical, walling-off effect of inflammation? Macroscopically certainly, at the site where the bacteria were deposited inflammation appears earlier in the immune, allergic animal than in the non-immune control. This macroscopic observation, although it has tempted numerous investigators to regard it as conclusive, is, however, not sufficient to force the belief that it was the formation of an obstructing wall of inflammatory exudate

which mechanically held the bacteria at the site in the immune animal for, as stated above, we had previously shown that when conditions are arranged so that an identical type and degree of inflammation occurs with the same rapidity at the site where bacteria lodge in the non-immune animal, the spread of bacteria is not inhibited at all (7), and furthermore, that when immunity is established without allergy the amount of inflammation at the site in the immune animals is, at each stage, far less than it is in the non-immune ones, and yet the bacteria remain perfectly immobilized at the spot (10). Those experiments indicated plainly that the immediate immobilization of bacteria in the immune body was the result not merely of inflammation but rather of some more specific process peculiar to the state of immunity.

On microscopic study of the sites of infection removed at various intervals, profound differences between the distribution and movement of the bacteria in the immune and in the non-immune body became apparent at once—differences which made it clear that forces preventing the spread of bacteria in the immune body are in play before any appreciable microscopic inflammatory reaction makes its appearance. Briefly, it was perfectly plain that in the immune animal the bacteria simply remained at the spot where they were injected, as though stuck fast to the cells and fibres of the tissues, in contrast to the manner in which they drifted freely from the site through the tissues in the non-immune animal. To begin with, it was observed that regardless of how highly immunized the animal might be (and the immunity was found to be completely effective in the face of several million lethal doses, which was as far as the tests were carried) the bacteria invariably proliferate for a while in the immune body, so that after the lapse of several hours they have multiplied many times. Their manner of growth in the immune is, however, very different from what it is in the non-immune animal. In the tissues of the latter, as the pneumococci divide, each pair of daughter cells immediately separates from the others and drifts away freely through the tissue spaces, whereas in the immune animal the pneumococci remain adherent to each other after division, so that clumps and chains are formed until, with the passing of time, little colony-like tangled masses of cocci are produced. As one follows the course of

events from moment to moment, therefore, the first difference that becomes apparent between the reaction in the immune and the non-immune animal is the formation of minute clumps of pneumococci in the former and the complete absence of clumping in the latter. This is plainly observable as early as thirty minutes after the bacteria have been deposited in the tissues (Figs. 1 and 2). Within an hour the clumps in the immune animals are distinctly larger, and well developed skein-formation serves to indicate the proliferation of the pneumococci, whereas in the non-immune animals in spite of an obvious increase in numbers of organisms only separate pairs of cocci are seen (Figs. 3, 4, 5, and 6). In addition to this difference in manner of growth of the bacteria in the immune and in the non-immune tissues, sections made from areas progressively further away from the site of injection show that in the non-immune animal the drift of pneumococci from the site is continuous from the time of their injection, so that after several hours they may be found in abundance 10 centimeters or more from the site where they were deposited, whereas, in sharp contrast, in the immune animal the bacteria remain until they are destroyed almost precisely where they lodged. Indeed, in highly immunized animals no pneumococci whatever can be found at any stage of the infection in any sections other than those passing directly through the spot corresponding to the bleb raised by the injection of the tenth of a cubic centimeter of culture; and even in those sections the pneumococci do not extend from end to end of the two-inch strip, but are sharply confined to an area limited by the diameter of the injected bleb of fluid. Further along in the section on either side of this area no pneumococci whatever are to be found. It is indeed most astonishing to observe how immediately and completely the bacteria are immobilized at the site where they first touch the tissues of the immune body.

As for the relation of inflammation to this process of local immobilization of bacteria, it may be said at once that both the clumping of the pneumococci and their adherence to the site are clearly in evidence before any appreciable inflammation appears. Both of these phenomena are very plainly apparent as early as thirty minutes after the bacteria have reached the tissues and at this period, even in the most highly allergic of the animals, the amount of inflammation at the site is negligible. There is not even enough capillary dilatation at this time

to give a pink color to the white skin, and microscopically no fibrin can be stained in the tissues, and at the most one sees only an occasional polymorphonuclear leucocyte here and there near capillaries from which they have just escaped. Indeed, even at the end of two hours the inflammation at the spot is trifling in amount (Figs. 7 and 8), and offers no suggestion of a restraining wall of exudate about the bacteria, nor is a single lymphatic or blood capillary obstructed by thrombosis.[2] At the end of four hours inflammation is well established in the allergic animal, and large clumps of pneumococci are found lying in the centre of an oedematous area which is surrounded by leucocytes. The tissue in this oedematous area where the pneumococci are concentrated becomes necrotic, and the leucocytes remain for a time at the periphery, as though the bacteria were giving off some poisonous substance which destroyed tissue and prevented the approach of the leucocytes. The latter, however, draw closer and closer until at length, after a lapse of 12 to 24 hours, the clumps of pneumococci are covered by phagocytes and are eventually engulfed and destroyed. The necrotic tissue becomes liquefied and the result is a typical, circumscribed abscess.

The sequence of events in the non-immune animal differs from the above in that several hours longer are required for the inflammation to reach the same degree of intensity at the immediate site of infection for, since the pneumococci neither adhere to each other as they proliferate nor remain sharply localized at the spot where they lodge, but instead drift freely through the tissue spaces, the inflammation is a diffuse and spreading one from the beginning. Furthermore, there never appears a leucocyte-free, oedematous, necrotic area immediately

[2] In a series of papers, Menkin (18) has laid great stress upon thrombosis of lymphatics as an explanation of the immobilization of bacteria and particulate matter deposited in an area of sterile inflammation. Except when very large doses of bacteria were injected leading to severe tissue damage and violent inflammation, thrombosis of lymphatics has not been encountered in the present experiments; and recently, Field, Drinker and White have, by careful direct measurements of lymph pressure, demonstrated that "under conditions of sterile inflammation such as have been produced here, there can be no question of generalized lymphatic thrombosis during the periods of observation, which were often 8 hours in length. The lymph flow (from the area of inflammation) is enormously increased" (*Jour. Exp. Med.*, 1932, lvi, 363).

surrounding the bacteria, such as is observed in the immune animal. From the beginning of the inflammation, bacteria and leucocytes are intermingled everywhere, but phagocytosis of the pneumococci is very slight and practically all of the bacteria are found extracellularly throughout the entire duration of the infection.

As one watches the development of the lesions in the immune and in the non-immune animals, it becomes perfectly clear that the fact that the pneumococci remain where they are placed in the immune tissues and grow in clumps at that spot is responsible for the fact that they are later sharply surrounded by a wall of leucocytes; whereas, the fact that they drift diffusely through the tissues of the non-immune body is responsible for the diffuse, spreading inflammation which occurs in that case. In other words, the wall of leucocytes is formed about the bacteria *because they remain concentrated and stationary in one spot*, rather than that the bacteria remain at the spot primarily because the wall of leucocytes prevents their escape, as is ordinarily stated. Undoubtedly, when it is finally formed, the abundant inflammatory exudate plays an important and essential rôle in maintaining the localization of the infection, both through its mechanical effects and through the destruction of the bacteria by the phagocytes; but the study of the present material leaves no doubt whatever that, even in the highly allergic body, there is no question of the bacteria being primarily held at the immediate site by a mechanical, walling-off effect of inflammation or by thrombosis of the channels which drain the area. The bacteria simply remain sharply where they are placed in the immune body as though tightly adherent to the tissues at the spot, and inflammation develops later about them.

The local fixation of bacteria in the absence of allergic inflammation. If the independence of this primary local fixation from the process of inflammation is obvious in the allergic body in which inflammation is accelerated and exaggerated, it is most strikingly clear in the immune, non-allergic body. Several years ago, Rich and Brown (10) showed that in pneumococcal infection immunity could be clearly separated from allergic inflammation by injecting the serum of an animal, immune and allergic to the pneumococcus, into the veins of a normal one. The immunity was transferred, but not the hypersensitiveness. When such passively immunized animals were infected intracutane-

ously with virulent pneumococci, their tissues were found to be remarkably indifferent to the presence of the bacteria. Far from exhibiting the exaggerated allergic inflammation which has been so widely assumed to be necessary for preventing the spread of bacteria and for effecting their destruction, the passively immunized animals, which never developed a septicaemia and invariably survived, showed at each stage of the infection far *less* inflammation than even the normal controls in which the bacteria spread rapidly from the site and produced a fatal, septicaemic infection. Indeed, it was ordinarily almost impossible to see any lesion whatever macroscopically at the site of infection at any time after the bleb of fluid produced by the injection of the bacteria had been absorbed. A series of animals was therefore passively immunized in the present study in order to trace the fate of the pneumococci in immune tissues in which inflammation was so inconspicuous, and the tissues preserved from the former experiments were restudied from this standpoint. It is unnecessary to enter into any lengthy descriptive details further than to say that the clumping and adherence of the bacteria to the tissues of these passively immunized animals was, with the greatest clarity, seen to be entirely independent of inflammation, for at each stage of the process the amount of inflammation was only the merest fraction of that which occurred in the allergic animals; and yet the bacteria remained sharply confined to the site at which they were deposited until the slight microscopic inflammation appeared, and the relatively insignificant outpouring of polymorphonuclear leucocytes was sufficient to dispose efficiently of several million lethal doses of the pneumococci, all of which remained immobile where they were deposited until the leucocytes had time to approach and to engulf them.

The mechanism responsible for the adherence of the bacteria to the tissues at the site of infection. That the bacteria stick fast where they lodge in the immune body is perfectly clear from a study of the present material, and it is equally clear that a mechanism which prevents them from drifting from the site is in operation before any effective amount of inflammation appears. The precise nature of this immobilizing mechanism cannot at present be stated with certainty. It is clear, however, that the factor responsible for the immediate immobilization is contained in the body fluids, for the phenomenon occurs

brilliantly in the passively immunized body, or, indeed, if bacteria and immune serum are mixed and injected immediately after mixing. It is therefore evident that the immobilization is a specific process dependent upon the immune antibody. Indeed, if one takes five rabbits and gives, intravenously, to the first 10 c.c. of antipneumococcal serum, to the second 4 c.c., to the third 2 cc., to the fourth $\frac{1}{2}$ cc., and to the fifth none at all, and then infects all of them intracutaneously with the same dose of pneumococci, both the degree of spread of bacteria from the site and, therefore, the area of the resulting lesion, will be found to vary inversely with the concentration of circulating antibody. It is, therefore, apparent that one of the very important functions of the immune antibody is the prevention of the spread of bacteria from the site where they lodge (Figs. 9, 10, 11, 12, 13).

Certainly, one factor which must interfere with the spread of the bacteria in the immune body is the formation of clumps which, undoubtedly, are not able to move as freely through the narrow tissue spaces as are single bacteria. In the tissues of the immune animal the pneumococci grow exactly as they are well known to grow in immune, agglutinating serum—that is, instead of each pair of daughter cells immediately separating from the others after division and drifting away diffusely through the medium as they do when growing in normal serum, the bacteria growing in an agglutinating serum adhere to each other after division and grow, therefore, in long, twisted chains and in colony-like masses. It is exactly this latter form of growth which occurs in the tissues of an immunized animal, and it becomes apparent at once that the presence of agglutinin changes, in effect, a microörganism which has a tendency to spread and to drift as it grows, into one which grows in relatively immobile, staphylococcal-like clumps in the tissues and therefore gives rise to lesions which are localized, in contrast to the diffuse, spreading lesions produced in the non-immune body in which the daughter cells of the proliferating pneumococci separate from each other and drift freely through the tissue fluids.[3]

[3] It is of considerable interest in this connection that most staphylococci do not *by nature* grow in large clumps in fluid media. In ordinary media they tend rather to grow as separate cocci or in pairs or short chains, clouding the medium diffusely. However, the serum of normal human beings is said to contain agglutinins

For many years the significance of agglutination has been a perplexing question, for the agglutinating titre of the serum does not always parallel survival immunity. Thus, an immunized animal with no demonstrable (or should one say *demonstrated?*) circulating agglutinins may survive relatively large doses of virulent organisms. It is because of this that it has been stated so often that agglutination bears no relation to immunity. Agglutination, however, is not an unimportant and accidental phenomenon totally uncorrelated with immunity. While I do not mean to imply that the phenomenon of local fixation of bacteria which is here described involves no process other than the formation of clumps through agglutination, agglutination nevertheless is a mechanism which can act to assist greatly the localization of the infection by means of its power of preventing the separation of multiplying bacteria.

But this factor of interference of drift of bacteria through the formation of clumps is, alone, hardly sufficient to explain the extraordinary imprisonment of the bacteria within the limits of an area a few millimeters square, for it requires time for the formation of large clumps, and bodies larger than the minute early clumps can move readily through the tissue spaces. On studying these sections one cannot escape the impression that in the immune body the bacteria from the very beginning actually adhere to the tissues with which they first come into contact. It seems quite possible that, just as the bacteria when covered with antibody adhere to themselves (agglutination) (15) and to the surface of the leucocyte (opsonization), as shown so well by Mudd and his co-workers (12), Kite and Wherry (13) and others, so may they also adhere to the cells and fibres of the tissues where they lodge. I have attempted to determine *in vitro* whether pneumococci adhere to fragments of connective tissue more conspicuously in immune serum than in a medium of normal serum, but

for staphylococci, and in media containing normal human serum the organisms are said to stick together and to grow in clumps which fall to the bottom and leave a clear supernatant fluid. It becomes evident, therefore, that what has been said above regarding the action of antibody in localizing infection may possibly apply even to the well-known tendency of staphylococci to grow in clumps and to produce localized lesions in the human body. We are at present engaged in an examination of this possibility.

although in general this did seem to be the case, the fact that the bacteria in the process of agglutination tend to entangle and therefore to cling to the fibrils has made it difficult as yet to strive at a satisfactory result. This entangling process itself must undoubtedly serve as an added factor in the immobilization of the bacteria *in vivo*. Whatever may be the ultimate explanation of the fact, however, the comparison of the sections of the early stages of the infection in the actively and passively immune with those of the non-immune animals leaves no doubt that under the specific influence of the immune antibody, and independently of inflammation or of lymphatic obstruction, the bacteria are held fast at the immediate site where they lodge as though actually adherent to the fixed cells and fibres of the tissues.

DISCUSSION

One cannot study the fate of the bacteria in material such as is described in this paper without realizing that one is witnessing the operation of an astonishingly effective protective mechanism possessed by the immune body. The view that it is the mechanical effect of inflammation which is primarily responsible for the prevention of spread of bacteria in the immune body, although widely accepted, has never been a satisfying one, were it only for the reason that it is perfectly well known that the rapidity of movement of bacteria through the tissues is such that even an accelerated allergic inflammation appears too late to effect that complete prevention of early movement which is so striking an attribute of immunity. This fact, however, has been ignored by those who maintain that the movement of bacteria is primarily prevented by inflammation, even though their own experiments frequently show the fact plainly, as we have pointed out in another place (7). That inflammation, once established, can inhibit the movement of bacteria is perfectly well established by the experiments of others (8), (5), (14), as well as by our own (7). This fact has, indeed, been known for forty years but, as discussed in the introduction of this paper, the experiments which demonstrate it really do not touch the question as to what prevents the *immediate* spread of bacteria in the immune body before an effective amount of inflammation has appeared. Between the moment of lodgment of bacteria in the immune body and the appearance of an effective amount of inflamma-

tion there is a period of time long enough to permit the progressive spread of the bacteria from the site, were inflammation the sole mechanism available to prevent their spread. In the non-immune body, indeed, they do spread far from the site even in the presence of inflammation appearing as rapidly and abundantly as allergic inflammation (7). The theory of fixation by inflammation has always left unexplained the striking immobilization of bacteria in the immune body during the pre-inflammatory period. The present observations, by bringing to light the existence of a potent immobilizing mechanism which is independent of inflammation serve to fill this gap in our knowledge in the case of pneumococcal infection. The question as to how far this phenomenon extends to other infections must await further study, but it seems altogether probable that this mechanism is in operation in all infections in which the immediate spread of bacteria is prevented in the immune body.[4] Similar studies on the fate of bacteria in the naturally immune body are at present in progress.

Some years ago, Opie reported important experiments which led him to the conclusion that foreign animal protein such as egg albumen is held fixed at the site of injection in an animal previously sensitized to that protein, and he suggested that specific precipitation might be a factor in preventing the diffusion of the protein. Subsequent experiments led him to the conclusion that when the foreign protein antigen and the serum of a sensitized animal, neither of which is appreciably irritating to the normal body, are mixed together, a precipitate is formed which produces inflammation when injected into the tissues of a normal animal. It was to the formation of this irritating precipitate that he ascribed the allergic inflammation which occurs when a foreign protein is injected into the sensitized body, and he regarded this allergic inflammation as very important in localizing the protein

[4] Shortly after the publication of an abstract of the present experiments (9), Cannon and Pacheco reported experiments from which similar conclusions were drawn regarding the primary importance of antibody in localizing the staphylococcus in immunized rabbits (Am. Jour. Path., 1930, VI, 749). This paper is of importance both because a different bacterium was used and because it comes from investigators who had previously concluded that the localization of staphylococcal infection in the immune body is accomplished by allergic inflammation (Arch. Path., 1930, ix, 1294).

at the site—a belief which he subsequently extended to the immobilization of bacteria in the immune body (5). Opie's observation of the formation of an irritant when foreign protein antigen and immune serum come into contact is an extremely important one, and of very great significance to the student of allergic inflammation. It is of importance, however, to record that we have so far been unable to extend it to infection with intact bacteria, for whereas allergic sensitivity to foreign protein can readily be transferred passively, we have shown that passive transfer of the serum of an animal allergic and immune to the pneumococcus established strong immunity, the bacteria were agglutinated in the tissues, but allergic inflammation did not occur (10); and, indeed, when the pneumococci were mixed with the immune serum *in vitro* and then injected into the skin of a normal animal, in spite of the brilliant agglutination the amount of inflammation produced was far *less* than when the same number of bacteria were injected into the allergic or even into the normal body. Under both of these conditions of passive transfer of antibody the bacteria were held rigidly at the immediate site, and the animals invariably survived with inconspicuous lesions and without the occurrence of bacteriaemia; and this in spite of the greatly reduced amount of inflammation. It is possible that under different conditions an irritant may be produced by the contact of bacteria and immune serum, as it was in the case of the mixture of foreign animal protein and immune serum in the experiments of Opie: or it may be that in pneumococcal allergy the allergic antibody is attached directly to the tissue cells, as Rich and Lewis have shown to be the case in allergy to tuberculoprotein (17), and that too little remains free in the circulation to render a mixture of antigen and immune serum effective as an irritant. But whatever may be the explanation of the *reduced* amount of inflammation at the site of injection of mixtures of bacteria and immune serum, as contrasted with the exaggerated inflammation observed by Opie in his experiments with foreign animal protein, the experiments serve as additional and important evidence that the exaggerated inflammation of allergy is not necessary for the fixation of bacteria at the site of infection in the immune body. Indeed, in subsequent experiments carried out for another purpose in collaboration with Miss Clara McKee, we have had the opportunity to observe repeatedly that in

the immune body the primary mechanism of fixation described in this paper is totally independent of any inflammatory reaction, for this process of specific fixation occurs in the most striking way in animals in which every trace of inflammation and inflammatory exudate has been suppressed (16).

CONCLUSIONS

In the non-immune body pneumococci drift freely through the tissues from the site where they are deposited and readily invade the blood stream. In the actively or passively immunized body the bacteria are held sharply at the immediate site where they lodge. The local lesion in the immune body is therefore limited in size, and septicaemia, with the attendant opportunity for metastatic infection, does not occur.

The immediate local immobilization of the bacteria in the immune body is accomplished by the specific action of the immune antibody which, through its effect upon the bacteria, causes them to remain fixed to the tissues at the site where they lodge until they can be surrounded and destroyed by the leucocytes. In this action the immune antibody performs an important and hitherto undemonstrated protective function.

The process of immediate fixation of bacteria in the immune body occurs independently of inflammation, and is in operation before any effective amount of inflammation is established at the site. Inflammation, when finally established, is, of course, of great importance in contributing to the localization of the infection and in effecting the destruction of the bacteria, but it is shown that the accelerated and exaggerated inflammation of allergy is not required for the successful performance of either of these two protective functions.

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EXPLANATION OF ILLUSTRATIONS

(Photographs by Mr. Milton Kougl)

FIG. 1. Site of infection in non-immune rabbit 30 min. after injection of pneumococci. The bacteria are scattered diffusely through the tissues, always as single diplococci and never in clumps. At this early period they have already drifted to a distance from the site where they were injected.

FIG. 2. Site of infection in immune rabbit 30 min. after injection of pneumococci (same dose and suspension as used in rabbit of Fig. 1). The bacteria are confined rigidly to the site where they first touched the tissues and clump-formation is well under way.

FIG. 3. Site of infection in non-immune rabbit 2 hours after injection of pneumococci (same dose and suspension as above). There has been a considerable proliferation of the bacteria and they have spread through the tissues from the site of infection, but they are always found as separate diplococci, never in clumps.

FIG. 4. Pneumococci growing in twisted skein in immune animal 2 hours after infection (same dose and suspension as above). No cocci have drifted from the immediate site where they first lodged. There are many such clumps at the site.

FIG. 5. Site of infection in non-immune rabbit 4 hours after injection of pneumococci (same dose and suspension as above). Multiplication of the bacteria is advanced and they have spread still further from the site where they lodged. There are no clumps—only separate diplococci.

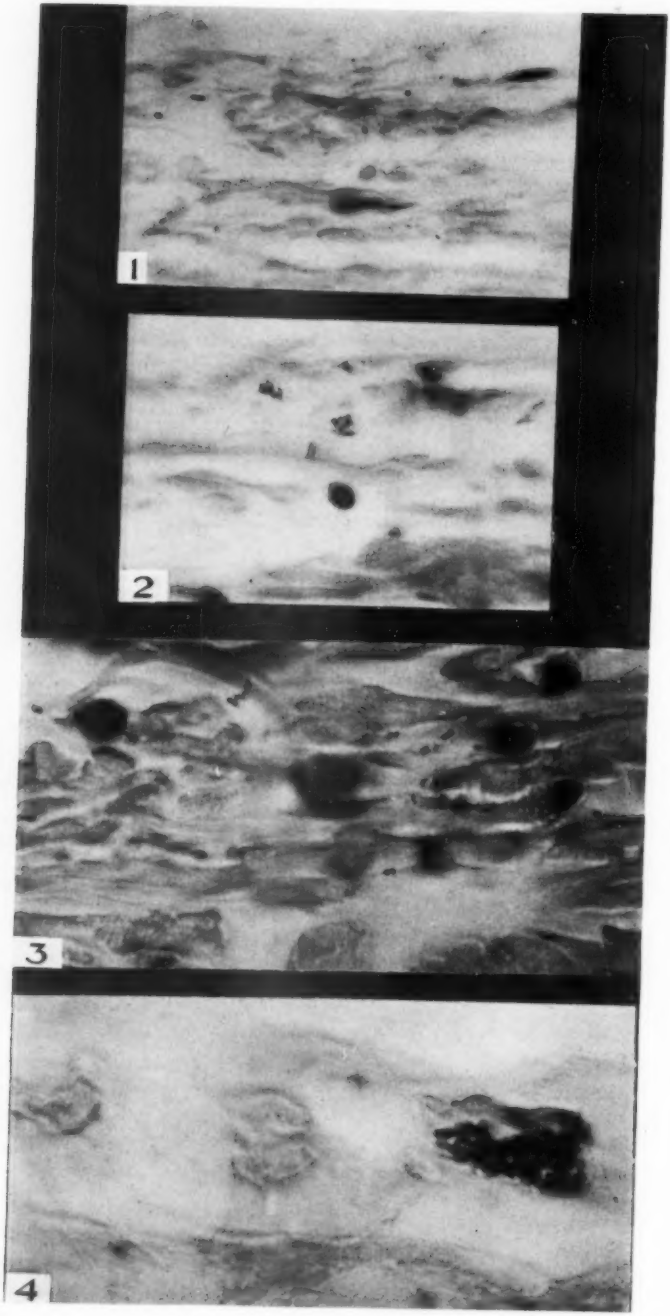
FIG. 6. Colony-like mass of proliferating pneumococci in immune rabbit 4 hours after injection of same dose and suspension as that used above. There are numerous clumps of this type at the immediate site of infection and no pneumococci whatever in the tissues except at the immediate site.

FIG. 7. Low power of site of infection in immune, allergic rabbit 2 hours after injection of pneumococci (same section as Fig. 4) to show the slight degree of inflammation. There is a slight scattering of leucocytes in the tissue. Venous and lymphatic channels are perfectly normal and unobstructed. The bacteria,

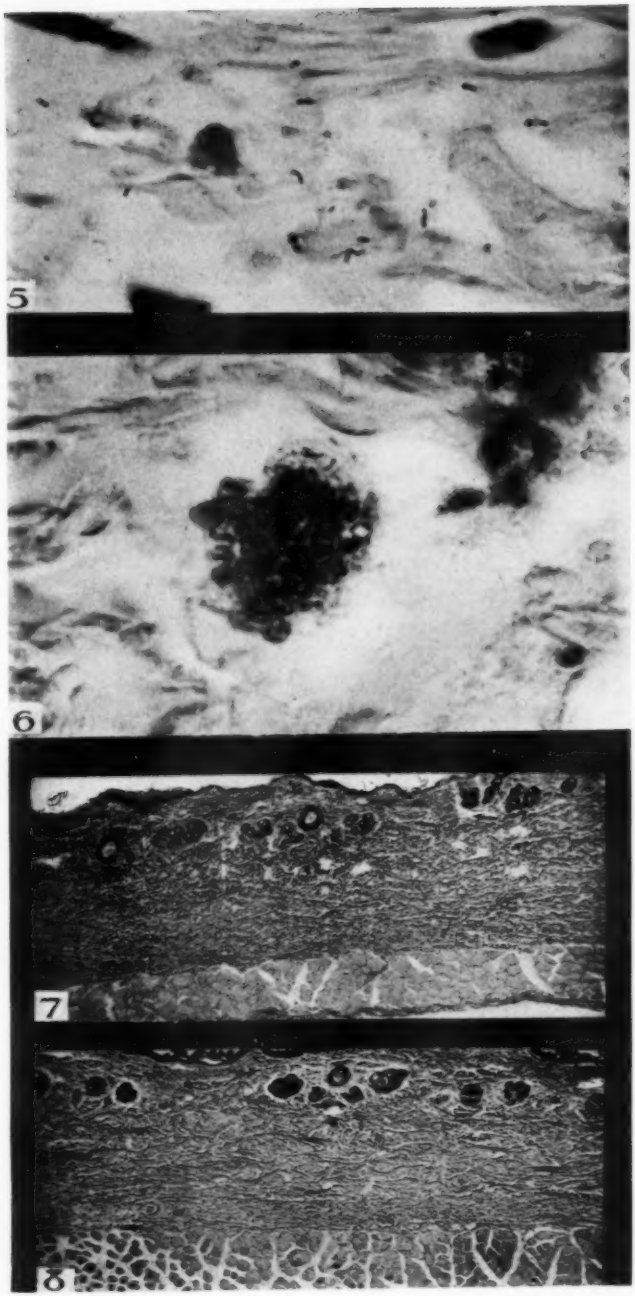
for the most part in clumps, are sharply localized to the immediate site of the injection.

FIG. 8. Low power of site of infection in non-immune rabbit 2 hours after injection of pneumococci (some section as Fig. 3). There is a slight degree of inflammation with a few leucocytes in the tissues. The bacteria are found scattered all through the section.

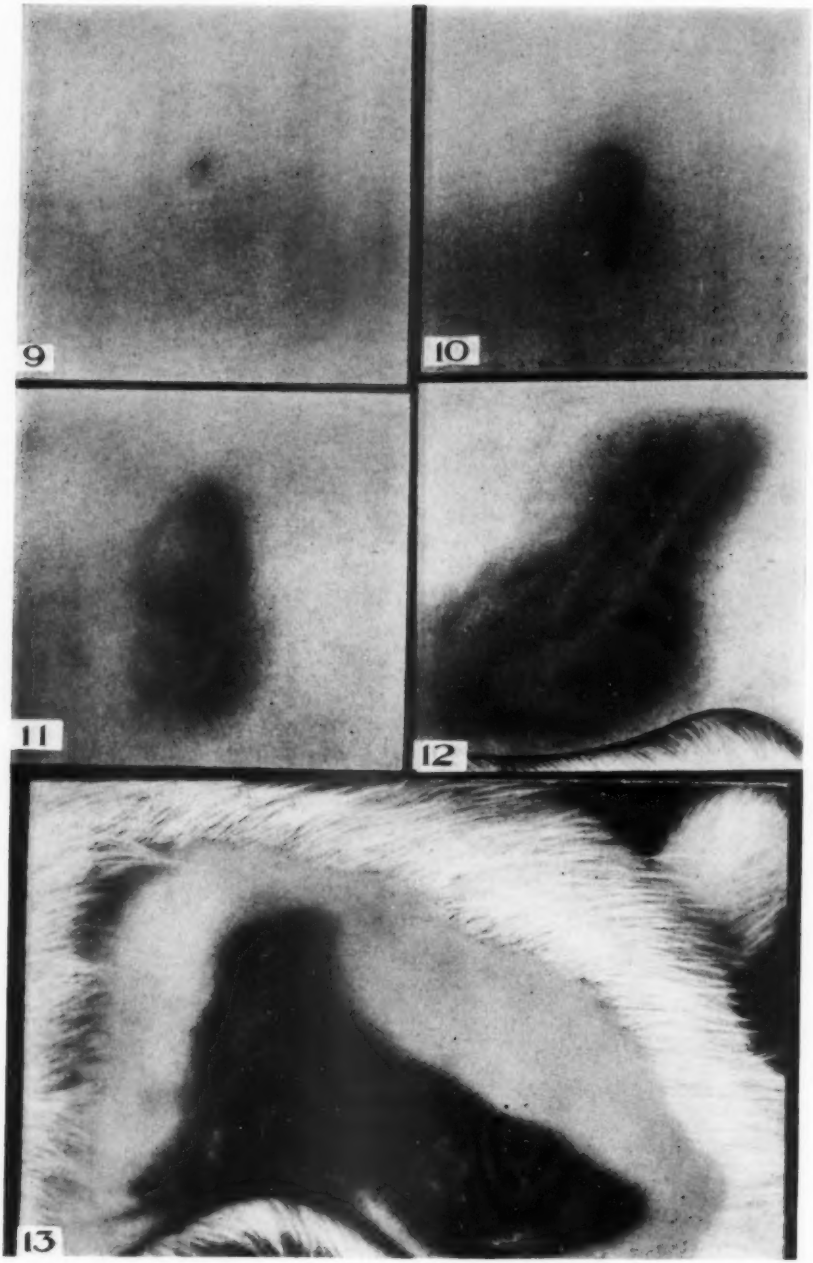
FIGS. 9, 10, 11, 12, AND 13 (Drawings by Mrs. Margaret Palmer). Sites of infection 22 hrs. after intracutaneous injection of 0.1 c.c. of a 1 to 1 dilution of a highly virulent culture of Type I pneumococcus. Three hours before injecting the pneumococci the rabbits of Figs. 9, 10, 11, and 12 received respectively 10 c.c., 4 c.c., 2 c.c. and ½ c.c. of immune serum intravenously. The rabbit of Fig. 13 was a non-immune control. It will be noted that the rabbit receiving 10 c.c. of immune serum (Fig. 9) shows almost no gross reaction, and that the size of the lesions in the other animals increases in inverse relation to the concentration of circulating antibody. The blood culture of the control rabbit (Fig. 13) became positive several hours after infection and the animal died with a large and extremely haemorrhagic lesion 22 hrs. after infection, while being sketched. The blood culture of the rabbit which received ½ c.c. of immune serum (Fig. 12) was sterile 7½ hrs. after infection, but became positive the next day and the animal succumbed to the infection. The blood cultures of the other passively immunized rabbits (Figs. 9, 10, and 11) were never positive at any time; the lesions eventually healed and the animals survived. It is of interest that, if the infecting dose be somewhat smaller than that used in this experiment, even ½ c.c. of immune serum will suffice to protect the animal. It will survive, but the local lesion will be large.



FIGS. 1–4



FIGS. 5–8



FIGS. 9–13

AURICULAR FLUTTER WITH 1:1 RESPONSE[1]

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In auricular flutter, the rapid contraction of the auricles at a rate of from 200 to 375 times a minute is commonly associated with some degree of heart block. When the patient first comes under observation, the ventricles are usually responding to every second, third or fourth auricular beat. Higher grades of partial block are found, however, and occasionally complete auriculo-ventricular dissociation occurs, as in the case described by Jolly and Ritchie (10) in 1911, to which the term "auricular flutter" was first applied clinically. On the other hand, there is a small number of cases in which the ventricles receive the full number of auricular impulses and attain the rate of contraction of the rapidly beating auricles. Such a 1:1 response is usually transitory; it occurs whenever the refractory period of the A-V node becomes so brief that it is less than the length of one auricular cycle. It has been estimated by Lewis and his associates (17) that the refractory period of nodal tissue is 30 per cent higher than that of auricular muscle. During rapid stimulation of the dog's auricle, failure of ventricular response occurs at rates of about 300 to 350, when dropped beats are noted and, if the rate is further raised, a 2:1 block appears. To produce steady 2:1 response in the auricular muscle itself, however, it is usually necessary to raise the rate of stimulation to 450 or 500 per minute. In 1:1 flutter, the junctional tissues have been found to transmit stimuli up to a rate of 320 per minute (3), a higher rate of frequency than is recorded in any other type of cardiac arrhythmia, and one which must approach the theoretical limit, if the nodal tissues in dog and man are at all comparable. This group of cases, therefore, offers an unusual opportunity for the study of influences affecting the refractory state of the A-V node.

In the following pages, three cases are reported which presented themselves during the course of a single year on the wards of the

[1] Submitted for publication January 10, 1933.

Johns Hopkins Hospital. It so happens that during the preceding 15 years, during which one or more electrocardiograms were taken on 9,184 patients, no other instance of 1:1 flutter was recorded. The first case is of especial interest because of the variety of stimuli producing paroxysms, because of the prolonged period of observation in the hospital, and because, so far as can be determined, it is the only instance of 1:1 flutter established by electrocardiogram in which a complete autopsy has been performed.

CASE REPORTS

Case 1. C. C. Unit 39278. The patient, a colored woman of 40 years, entered the Johns Hopkins Hospital on September 23, 1931, with the complaint of nervousness and rapid heart beat. The family history was non-contributory. Her general health had been good, and she had worked as a cook. As a child she had had diphtheria and malaria, as well as mumps, measles and pertussis. In 1922 she had lobar pneumonia (Pneumococcus Type I) and was on the medical service of this hospital for a month. The course of her disease was uncomplicated. At that time there were no signs of hyperthyroidism, and the heart was considered normal. Cardiac dulness extended 9 cm. to the left in the 5th interspace, 3 cm. to the right in the 4th interspace. No murmurs were heard over the precordium. There was a chronic right aural discharge, which she had had for several years, and a pararectal abscess, which was later treated in the out-patient department. The Wassermann reaction was always negative, and there had been no history of syphilis nor of rheumatic fever. Menses began at 12 years and were always regular. She had married and her only pregnancy resulted in a child born at term, which died four days later.

Present illness. Her final illness began insidiously in 1929 with loss of weight; over a course of two years she gradually lost 47 lbs. Four months before coming to the hospital she noticed the onset of nervousness, weakness, anorexia, nausea and, for a few days, diarrhoea. Palpitation of the heart appeared, and she became short of breath on exertion. She grew steadily worse, so that late in August 1931 she was obliged to give up work and go to bed on account of swelling of the ankles and orthopnoea. After two weeks of bed rest, together with digitalis prescribed by her physician, she was considerably improved; her appetite returned, and she was able to be up and about. Her general condition of weakness and nervousness persisted, however, and on this account she came to our out-patient dispensary and was at once admitted to the medical ward.

Physical examination. T. 100.6°. P. 120. R. 26. B.P. 130/70. A restless apprehensive negress of 40 years, who had obviously lost weight recently. The skin was smooth, warm and moist. Both eyes were abnormally prominent and staring; all the classical thyrotoxic eye signs were present. There were bilateral

corneal opacities, and the left pupil was irregularly oval from old adhesions. Teeth and gums were in bad condition. There was no general glandular enlargement. The thyroid gland was diffusely enlarged and quite soft; a systolic bruit was present over the whole gland. The retromanubrial dulness was increased, measuring 8 cm. in the first interspace. There was a vigorous wavy impulse over the whole precordium. Over the base of the heart a diastolic shock was felt, sharpest in the pulmonic area. The area of cardiac dulness was increased to left and right, and the outline was rounded, extending to the left 7 cm. in the 2nd interspace, 10 cm. in the 3rd interspace, 12 cm. in the 4th interspace and 12.5 cm. in the 5th interspace. The maximum dulness to the right was 4.5 cm. in the 4th interspace. The heart sounds were regular and rapid, the first sound at the apex was not very loud, and was followed by a systolic murmur which was also audible along the left sternal border and was loudest in the pulmonic area, where it assumed a scratchy quality. The second sound was markedly accentuated in the pulmonic area. Blood pressure 130/70. Peripheral vessels not notably thickened. The liver descended one finger-breadth below the right costal margin. There were no râles at the lung bases, and no sacral or tibial oedema. A hard, rounded mass was palpable above the symphysis, apparently a myoma of the uterus. There was a fine tremor of the extended fingers. Neurological examination negative.

Laboratory tests. Urine: S. G. 1.008–1.022. Acid. Occasional trace of albumin. No sugar. A few white blood cells, no casts or red blood cells in the sediment.

Blood count: R.B.C. 3,940,000. Hgb. 78 per cent. W.B.C. 4,950. P.M.N. 40 per cent. Lymph. 55 per cent. Mono. 4 per cent. Eos. 1 per cent.

Blood Wassermann reaction: negative.

Basal metabolic rate: +63 on admission.

X-ray of chest: Heart very much enlarged. Aorta dilated. Mediastinal shadow extends up into neck, probably due to substernal thyroid. Secondary changes in the lungs. Teleo. measurements: M.R. 4.9 cm. M. L. 10.8 cm. T. 22 cm.

Blood chemistry: Sugar 92 mgm. per cent. N-P-N. 34 mgm. per cent.

Throat culture: Beta hemolytic streptococcus in almost pure culture on October 2nd.

Electrocardiogram: Normal sinus rhythm. Rate 100. P-R interval 0.16 second.

Special examinations. Laryngoscopic: vocal cords move normally and are not congested.

Dental: marked oral sepsis, with two abscessed teeth, slight gingivitis and destruction of peri-dental tissues.

Course in the hospital. On admission the clinical impression was exophthalmic goitre of some severity, with myocardial insufficiency which had apparently been more marked before the period of rest in bed at home. She was placed on a régime

of complete rest, with amplified diet and small doses of luminal. During the first two weeks, she had a daily rise of temperature to 101–102°, associated with moderately inflamed throat from which beta hemolytic streptococcus was cultured. On October 16, after ten days of normal temperature, Lugol's solution, 1 cc. three times a day, was started; at that time the B.M.R. was +45, the daily pulse range from 85 to 125 per minute. The cardiac signs had not changed, save that a continuous murmur in the second interspace to the left of the sternum, a distinctly audible third sound, and a late diastolic roll were each described by one or more observers. It was considered that the cardiac signs represented more than the changes produced by hyperthyroidism alone, and the possibility of a patent ductus arteriosus or mitral stenosis was discussed, but no definite conclusion reached. On October 18, the patient complained of "bumping" of her heart but was not very uncomfortable. The pulse was found to be irregular, with groups of regular beats, and a rate of 120 to 130 per minute. The electrocardiogram showed auricular flutter, with 2:1 and 3:1 grades of heart block producing varying ventricular response. For the remaining seven months of the patient's life, auricular flutter remained the dominant rhythm with one interlude of auricular fibrillation. Clinically, the pulse varied almost hourly between a rapid, regular rhythm corresponding to a 2:1 response of the ventricles at a rate of 150, and an irregular, slower rhythm produced by continually varying grades of block. The patient was digitalized, but the amount of drug given was never pushed beyond the stage of minor intoxication signalled by nausea and occasionally by vomiting.

Under iodine therapy, the basal metabolic rate fell to +19, the patient gained weight and was subjectively improved so that, despite the continuation of the auricular flutter, it was decided to attempt subtotal thyroidectomy. On November 11, avertin anesthesia was administered *per rectum*, but before the operation could be started, the patient's pulse rose to around 240, becoming almost imperceptible, the blood pressure fell to a systolic level of 60, and respirations temporarily ceased. Oxygen and artificial respiration were immediately administered, together with stimulant drugs; for over an hour the heart rate persisted at its high level with a few remissions, then returned to a rate of 136. The full significance of this episode as an expression of abnormal cardiac mechanism was not appreciated at the time; by mistake, the patient had learned of the operation and it was thought that the terrific tachycardia was due to the ensuing emotional upset.

Although the patient was none the worse for this experience, surgery seemed temporarily out of the question, and on November 27 and December 4 applications of radium were made over the thyroid gland; following the second radiation, the skin over the thyroid became superficially reddened and sensitive, and further radium therapy was postponed for fear of producing a serious burn. The B.M.R. gradually rose again to +57, despite the continued administration of iodine, so that by January 7, 1932, she had completely escaped from the first iodine remission; at this time Lugol's solution was discontinued. Subjectively, however, she was much better than on admission, the thyroid was smaller and firmer, and the tremor

and exophthalmos were diminished. During this period the pulse was frequently very irregular, with marked pulse deficit between apex and wrist, and on one occasion the electrocardiogram showed auricular fibrillation. Clinically, it was impossible to differentiate between auricular flutter with varying grades of block and auricular fibrillation, but the regular rhythm intervened so often that fibrillation could have occurred only paroxysmally.

After eight weeks without iodine, potassium iodide was started on March 2, in order to prepare the patient again for operation. The B.M.R. fell from +57 on February 27 to +22 on March 7. On March 8, following an emotional upset, the pulse again rose to about 250; an electrocardiogram was obtained, and it was found that the auricle and ventricle were both beating at 260 per minute—auricular flutter with 1:1 response. The attack promptly subsided. On March 12, the B.M.R. was +9, and on March 15 operation on the thyroid was again attempted. This time avertin was administered rectally without the knowledge of the patient. Nevertheless, thirty minutes later her pulse rose to 250, respirations became rapid and irregular with a period of apnoea lasting 45 seconds, and her blood pressure was unobtainable. Again she was revived with stimulants, and returned to the ward with her thyroid untouched. The paroxysm lasted about an hour. The pulse then fell to 130 and later to 94. Digitalis was stopped and 2 grams of quinidine were given daily for 15 days without success in terminating the auricular flutter. After 24 grams of quinidine had been administered, she had another attack of rapid heart rate for an hour or so, at approximately 225.

With the patient fully digitalized, and with a B.M.R. of +26, bilateral subtotal thyroidectomy was performed on May 7, 1932. Her condition was excellent throughout the operation; the pulse rate remained at 140. Immediately after the operation, the pulse rate rose to 260 two or three times, but none of these attacks lasted more than five minutes, nor were they alarming to the patient. Throughout the two days following operation she was surprisingly comfortable and rational, but her temperature rose to 106.4° on the morning of May 8, and thereafter swung between 103° and 106°. Again she had brief periods when her heart beat at 240. Her lungs remained clear; her condition was typical of a post-operative "thyroid storm." She seemed to be past the worst of it, however, when suddenly on the morning of May 9 she was found difficult to arouse, breathing was labored, and within a few minutes she died.

Post-mortem examination

Anatomical diagnosis. Exophthalmic hyperplasia of the thyroid; partial thyroidectomy. Enlarged thymus; large patent foramen ovale; history of auricular flutter; tricuspid insufficiency; hypertrophy and dilatation of the right auricle and ventricle; thickening of the pulmonary and mitral valves; epicardial thickening over the right ventricle; focal necroses in the liver; myomata in the uterus; pleural and peritoneal adhesions.

Dr. MacCallum's note on the heart. The heart is disproportionately large on the

right side. The left ventricle shows as a small appendage. The coronaries are somewhat tortuous. There is a thickening of the epicardium over practically the whole right ventricle, especially over the conus. The right auricle is enormous, and there is an open foramen ovale, 2 cm. in diameter, with practically no guarding membrane. The right auricular appendage is very large, and the right auricle taken all together is extremely capacious. The tricuspid valve is a good deal thickened along its margin, especially in the middle of its more anterior leaflet. It measures about 13 cm. in circumference. The chordae tendineae are rather thick and slightly shortened, especially to that anterior leaflet. The conus pulmonalis is extremely large and the wall of the ventricle there not more than 5 mm. thick, but the pulmonary valves are slightly thickened at their mid-point. The pulmonary artery is smooth but very large. The left auricle is about normal in size. The mitral valve shows some slight thickening at the insertion of the chordae tendineae, but it is perfectly competent. The ventricle measures only 6.5 cm. in length, and the wall is about 15 mm. in thickness. The aortic orifice is hardly 5 cm. in circumference. The septum membranaceum is intact.

The aorta is narrow; it measures 5.5 cm. in circumference in the ascending arch and only about 4 cm. in the descending portion. The ductus arteriosus is closed; one can see its point of origin.

Weight of organs

Heart	340 grams	
Thymus	10 grams	
Thyroid isthmus	33 grams	Removed at operation
Left lobe	60 grams	
Right lobe	46 grams	

Microscopic note. The thyroid shows diffuse hyperplasia typical of exophthalmic goitre. The thymus is hyperplastic. The myocardium is normal. There is definite pulmonary emphysema. There is central atrophy of the liver. The uterus contains myomata. The remainder of the microscopic examination added nothing of significance.

Summary. Briefly, the case is that of a negress of 40, who entered the hospital with exophthalmic goitre of two years' duration, and myocardial insufficiency appearing two months before admission. During her first month on the ward, the normal sinus rhythm of the heart (Fig. 1) was replaced by auricular flutter, which, in spite of all treatment, remained the dominant rhythm until her death seven months later. Either a 2:1 or 3:1 grade of block was usually present (Figs. 2 and 7); rapid alternation between the 2:1 and 3:1 response frequently resulted in an irregular ventricular rhythm (Fig. 3). On one occasion only, the electrocardiogram showed auricular fibrillation (Fig. 4). She had a number of paroxysmal attacks of 1:1 flutter (Figs. 5 and 6), with ventricles beating rhythmically at 250 to 260 times a minute. Partial removal of the thyroid gland was finally done under local anesthesia. The patient died suddenly of heart failure two days later,

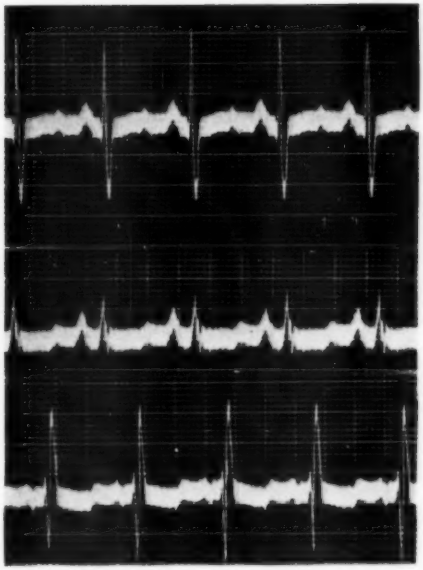

FIG. 1. ELECTROCARDIOGRAM TAKEN ON SEPTEMBER 30, 1931, SHOWING NORMAL SINUS RHYTHM (CASE 1)

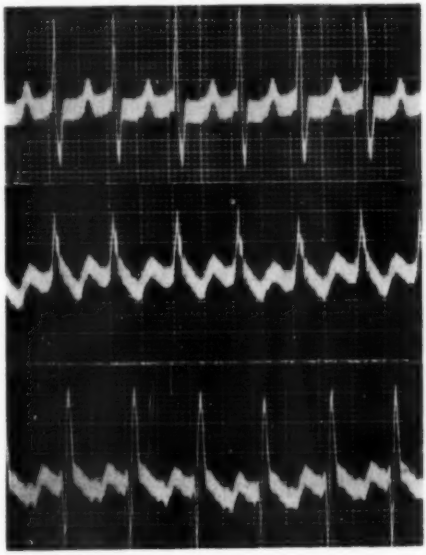

FIG. 2. RECORD TAKEN ON OCTOBER 20, 1931, SHOWING AURICULAR FLUTTER WITH 2:1 VENTRICULAR RESPONSE (CASE 1)

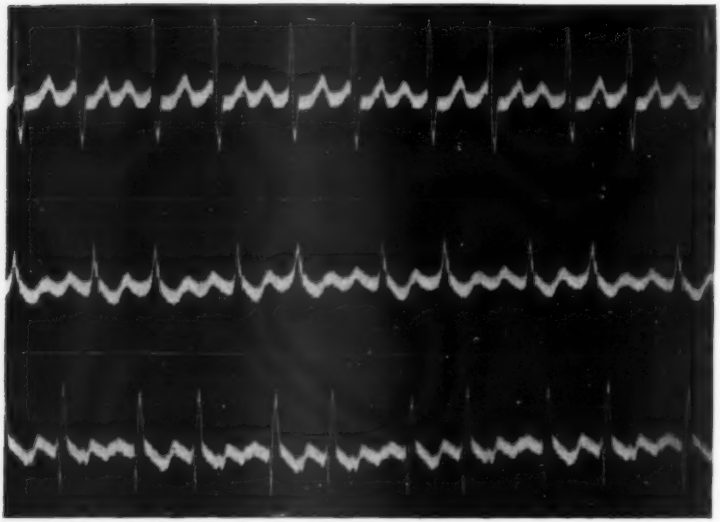

FIG. 3. RECORD TAKEN ON NOVEMBER 2, 1931, SHOWING AURICULAR FLUTTER WITH ALTERNATE 2:1 AND 3:1 VENTRICULAR RESPONSE (CASE 1)

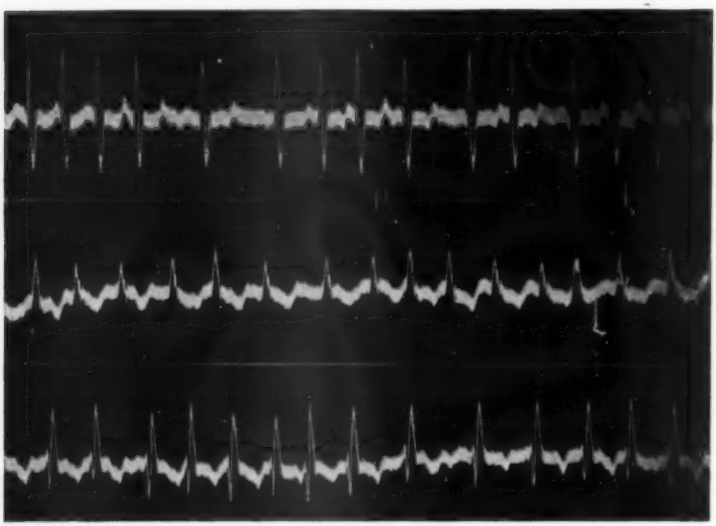

FIG. 4. RECORD TAKEN ON JANUARY 27, 1932, SHOWING AURICULAR FIBRILLATION (CASE 1)

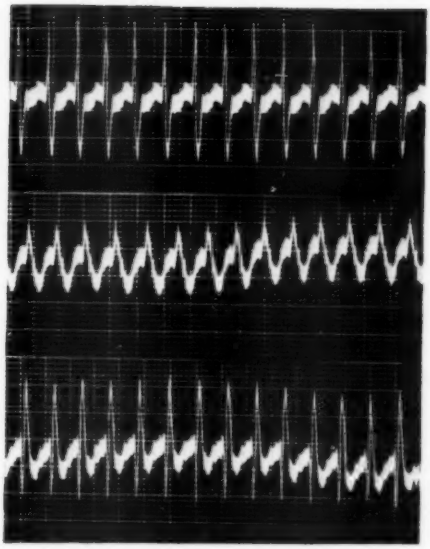

FIG. 5. RECORD TAKEN ON MARCH 8, 1932, SHOWING AURICULAR FLUTTER WITH 1:1 VENTRICULAR RESPONSE (CASE 1)

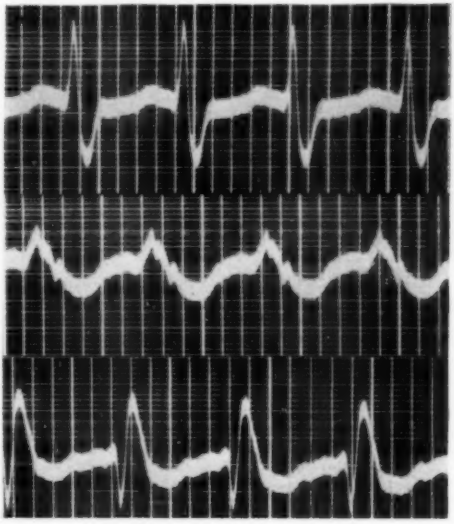

FIG 6. THE SAME AS FIGURE 5
The camera is running at high speed (Case 1)

during a post-operative hyperthyroid crisis. At autopsy, the right auricle and ventricle of the heart were found to be greatly hypertrophied and dilated, with a large patent foramen ovale. The thyroid gland was typical of those seen in exophthalmic goitre. There was also considerable emphysema.

Comment. Twenty electrocardiograms were taken during the patient's course in the hospital, as shown in Table I. In examining this table, one is at once struck by the steady decline in auricular rate from 300 a minute in Record 2, taken the day after the onset of flutter, to 252 a minute in Record 11, taken 5 months later. The gradual slowing of the auricles was not correlated with the level of the meta-

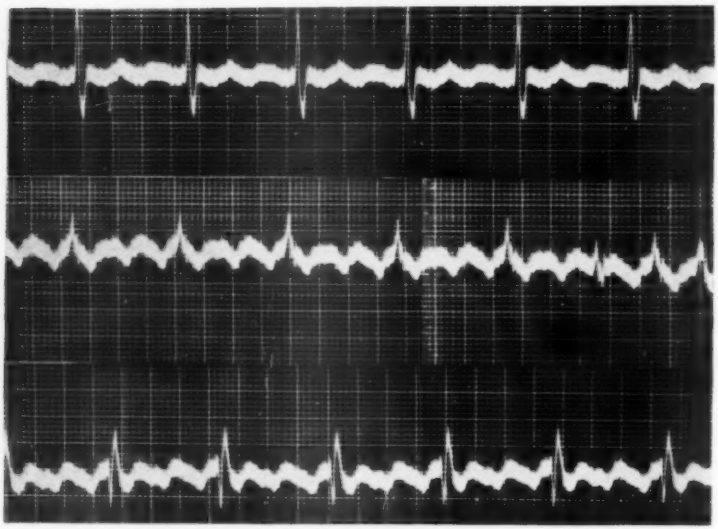

FIG. 7. RECORD TAKEN ON MARCH 14, 1932, SHOWING AURICULAR FLUTTER WITH 3:1 VENTRICULAR RESPONSE (CASE 1)

bolic rate, nor did it entirely parallel the degree of digitalization (31), since record 10, taken when the patient had been without digitalis for 10 days, fell in line with the others. Nevertheless, it is probable that the diminishing auricular activity was an expression of returning myocardial reserve produced by bed rest and digitalization. It has been found that the rate of the auricles in flutter remains remarkably constant over long periods. Parkinson and Bedford (22) report a case observed over a period of ten years in which the spontaneous variation in auricular rate was only 30 beats a minute. Whenever quinidine is used, however, the rate of the auricles in flutter is always decreased. This effect is illustrated in Table I,

TABLE I

Analysis of electrocardiograms, Case 1

RECORD	DATE	RATE PER MINUTE		RHYTHM	A-V BLOCK	B.M.R.	LUGOL'S	DIGITALIZATION	TOTAL QUINIDINE	REMARKS
		Auricles	Ventricles							
									grams	
1	9/30/31	100	100	Sinus	None	+58	None	None		One week after admission
2	10/19/31	300	115±	Auricular flutter	2:1 and 3:1		Day 4	Partial		Record taken day after onset of arrhythmia
3	10/20/31	300	150	Same	2:1	+44	Day 5	Complete		
4	10/21/31	300	150	Same	2:1		Day 6	Complete		
5	11/ 2/31	276	113.5	Same	Alternate 2:1 and 3:1	+20	Day 18	Complete		
6	11/18/31	272	136	Same	2:1	+21	Day 34	Partial		Thyroidectomy attempted; 1:1 paroxysm
7	1/27/32	Irregular	187±	Auricular fibrillation		+58	None	Partial		
8	2/ 1/32	272	120±	Auricular flutter	2:1 and 3:1	+50	None	Partial		
9	2/13/32	272	136	Same	2:1	+45	None	Partial		
10	3/ 8/32	260	260	Same	1:1	+22	Day 6	None		No digitalis for 10 days
11	3/14/32	252	90±	Same	2:1 and 3:1	+9	Day 16	Partial		Thyroidectomy attempted the following day; 1:1 paroxysm
12	3/22/32	230	115	Same	2:1	+3	Day 24	Partial	3	
13	4/ 1/32	230	100±	Same	2:1 and 3:1	+12	Day 34	None	19	No digitalis for 17 days
14	4/ 5/32	240	80	Same	3:1	+16	Day 38	None	30	
15	4/11/32	250	125	Same	2:1	+6	Day 44	Complete		
16	4/18/32	260	130	Same	2:1	+8	Day 51	Complete		
17	4/20/32	254	100.5	Same	Alternate 2:1 and 3:1	+12	Day 53	Complete		
18	5/ 5/32	272	104	Same	Alternate 2:1 and 3:1	+26	Day 68	Complete		
19	5/ 7/32	286	143	Same	2:1		Day 70	Complete		Record taken an hour before operation
20	5/ 7/32	260	109.5	Same	Alternate 2:1 and 3:1		Day 70	Complete		Record taken an hour and a half after operation

where the lowest rates, 230 to 240, were recorded during the course of quinidine therapy.

The ventricular rate and rhythm in auricular flutter are dependent upon the refractory state of the auriculo-ventricular node. In this case, a high grade of block was never established, despite full doses of digitalis, a circumstance which played a major rôle in the relative ease with which paroxysms of 1:1 response were produced. Eight of the records showed pure 2:1 response (Fig. 2), whereas only one record was obtained of uninterrupted 3:1 block (Fig. 7). Four records showed alternation of single cycles of 2:1 and 3:1 response (Fig. 3), and four showed these two responses irregularly interspersed, with the 2:1 block usually predominant. The latter rhythm is very difficult to differentiate from auricular fibrillation clinically.

The 1:1 paroxysms were produced in various ways. Emotional excitement was thought to be responsible on more than one occasion. One attack occurred after the patient had received 24 grams of quinidine sulphate in twelve days. Thyroidectomy had to be cancelled twice on account of paroxysms coming shortly after the administration of atropine 0.6 mgm. and morphine 10 and 16 mgm. hypodermically, and avertin 3 c.c *per rectum*. On the occasion when a paroxysm did not supervene before the operation was successfully completed, the patient was given atropine 0.6 mgm., morphine 12 mgm. and scopolamine 0.3 mgm. on the ward, and a local anesthetic (procaine 1:200) was used during the operation supplemented by nitrous oxide. Whether the avertin precipitated the paroxysms is difficult to say, but it surely contributed to the state of collapse which accompanied the attack. It seems not unlikely that even small amounts of atropine might have a profound effect on such a highly irritable A-V node, and that the patient was enabled to go through the operation without a paroxysm on the third attempt only because the node was in this instance completely under the influence of digitalis. The remaining attacks occurred post-operatively. As soon as the patient returned to the ward, a shower of brief paroxysms were noted, for which it would be impossible to assign any single cause. Two days later, during the peak of the post-operative "thyroid storm," the 1:1 response was observed for the last time. During her post-operative course there was high fever which, together with the other aspects of a tremendously elevated metabolism, must have resulted in cardiac exhaustion. This was the only time when a relationship appeared to exist between a high metabolic rate and an increased susceptibility to 1:1 attacks. All the other attacks occurred when the B.M.R. lay between +14 and +16, while none were noted during the weeks when her B.M.R. ranged from +44 to +58.

The functional patency of the foramen ovale at autopsy together with the marked hypertrophy of the right auricle and, to a lesser degree, of the right ventricle, leaves little room for doubt that a stream of blood must have passed from the left to the right auricle during life. In the face of the triple burden of congenital anomaly, increased demand upon the circulation due to the heightened metabolism and abnormal cardiac rhythm, it is amazing that any degree of cardiac efficiency

could be maintained, especially during 1:1 paroxysms. That such attacks were twice attended by circulatory collapse may be attributed to the additional embarrassment of the hypotensive action of avertin. During one episode of 1:1 response, the patient lay quietly without the slightest sensation of dyspnoea.

Case 2. H. K. Unit 45456. The patient was a white woman of 21 years admitted to the Obstetrical Service on September 20, 1932. The following day, her first pregnancy terminated in a normal spontaneous delivery. For the next few days her temperature ranged between 100° and 102°, with a leucocyte count of 22,840. On the afternoon of September 23, she noticed a "fluttering of the heart" over a period of ten minutes. At nine o'clock the next morning, while nursing her baby, she suddenly became aware of the fact that her heart was fluttering. She became weak and breathless, and it was found that her pulse rate was very rapid.

She said that she had been subject to similar attacks for about four years. On the first occasion, she was walking upstairs, when suddenly she felt dizzy and fainted; upon regaining consciousness, her heart was "fluttering," and continued to do so for about 24 hours. Since then she has had numerous similar episodes, none of them, however, as severe or prolonged as the first. They begin and end abruptly, usually precipitated by excitement or eating a heavy meal, and lasting about ten minutes. During the attacks she feels faint, but avoids loss of consciousness by lying flat on the floor as soon as the palpitation begins. She thinks that the attacks are aborted by taking baking soda. Between attacks she has been free from all cardiac symptoms. There is no history of rheumatic fever or chorea, but she has had sore throats not infrequently.

Physical examination. T. 101.6°. P. 220–250. R. 28. B. P. 70/65. A well nourished young white woman, very pale and quite cyanotic; she was obviously uncomfortable, but complained of no pain. There was some tachypnoea, but she lay flat in bed without true dyspnoea. The tonsils were large and pale. The thyroid was palpable but not appreciably enlarged. The lungs were clear throughout. The heart was difficult to examine properly on account of tender lactating breasts. There was no precordial bulge or heave. There was a visible and palpable impulse in the sixth left interspace 9.5 cm. from the midline. The sounds were very rapid, well over 200 a minute, and perfectly regular. No murmurs were heard. There was moderate engorgement of the cervical veins. The rapid carotid pulsation was quite conspicuous. The radial pulse was barely palpable; the vessel walls were delicate. Neither the liver nor spleen were palpable. There was no oedema. The remainder of the examination was non-contributory.

Course in the hospital. Tachycardia, weakness and shortness of breath continued throughout the day. An electrocardiogram taken at 11:30 a.m. showed a rapid, regular rhythm of supraventricular origin at a rate of 244 beats per minute. Another record taken at 3 p.m. showed the same complexes at a rate of 224 a minute; all attempts at vagal stimulation such as pressure in the neck, over the eyeballs, and over the abdomen, pulling out the tongue and drinking cold water,

failed to alter the rate or appearance of the complexes in any way. At 7 p.m. 4 ampoules of digifolin were administered. Between 9 and 10 p.m. the pulse rate

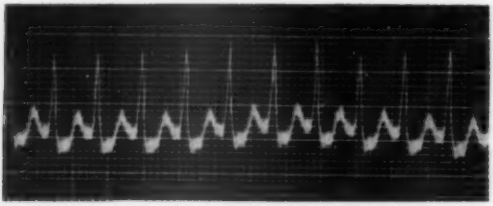

FIG. 8. LEAD I TAKEN DURING PAROXYSM. RATE 244 PER MINUTE (CASE 2)

FIG. 9. NORMAL SINUS RHYTHM (CASE 2)

suddenly fell to 106, and an electrocardiogram taken an hour later showed normal sinus rhythm with perfectly normal complexes.

Thereafter convalescence was uneventful; there were no further attacks of palpitation, and she was discharged from the hospital on October 3, after an

afebrile week. The day of discharge the B.M.R. was −3, the urine was normal, B. P. 112/78 and hemoglobin 80 per cent.

Comment. This case has been included because it provides an excellent illustration of a group of cases heretofore classified as 1:1 auricular flutter on a basis of rate alone. It will be further discussed below, together with others reported in the literature.

Case 3. W. M. Unit 45803. The patient was a negro farm laborer of 55 admitted to the medical wards on October 11, 1932, complaining of weakness, short-

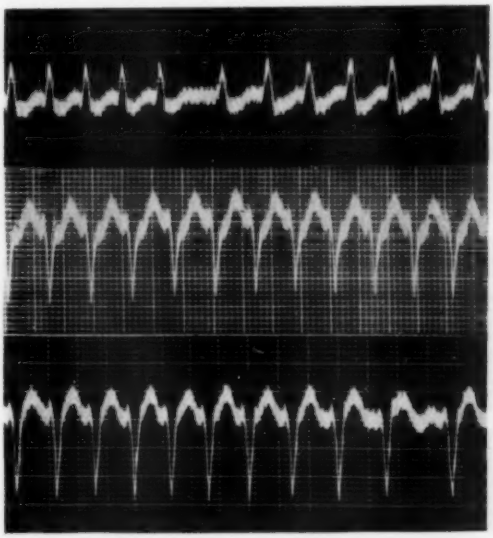

FIG. 10. 1:1 FLUTTER (CASE 3)

ness of breath and attacks of rapidly beating heart. In the past his health had been generally good. At the age of 18 his neck became enlarged symmetrically to such an extent that he could not close his collar He was told by a doctor that he had a goitre. There were no symptoms of hyperthyroidism, and a year later the swelling subsided. He had had gonorrhoea as a young man, but denied syphilis and rheumatic fever. More recently, he had had intermittent "sick headaches" prior to extraction of most of his teeth in 1928. From 1928 to 1931 he had several night-sweats a week. In December 1930 he had "influenza" for a week. Since that time he had gradually lost 37 lbs. of weight.

Ten years ago, while running during a 'possum hunt, he suddenly felt so weak,

breathless and exhausted that he had to sit down under a tree for an hour before he could catch his breath sufficiently to go home. Since then he has had no further difficulty until May 1932, when his breath started coming in gasps as he was plowing, and he was again forced to rest for half an hour before returning home. From then on he has been unable to work because exertion brought on similar attacks. He has had at least four severe ones, all coming on suddenly, lasting an hour or two, and wearing off gradually. During these episodes he was aware of rapid beating of his heart, but his attention was chiefly focussed on the dyspnoea and weakness; however, he never lost consciousness. Between attacks he felt moderately well on

FIG. 11. AURICULAR FLUTTER WITH VARYING A-V BLOCK (CASE 3)

restricted activity, but has been obliged to sleep propped up on pillows, a new departure for him. He was often aware of "skipping" of his heart.

Physical examination. T. 98.6°. P. 110. R. 18. B. P. 125/78. A rather frail mulatto, propped up in bed in no distress. There was evidence of recent weight loss. Respirations were easy; there was no cough or cyanosis. The retinal vessels were not appreciably altered. Four snags of teeth remained. The thyroid was not enlarged. The lungs were clear. The heart was a little enlarged, measuring 10.5 cm. to the left in the 5th i.s. and 4 cm. to the right in the 4th i.s. Retromanubrial dulness measured 6 cm. in the 2nd i.s. There were no precordial shocks

or thrills. A vigorous single thrust was visible and palpable 9.5 cm. to the left in the 5th i.s. The heart shifted 3 cm. on change of position. The sounds were tic tac in character; no murmurs were heard. The second sound was louder in the aortic than in the pulmonic area, but was not tympanitic. The rhythm was variable, at times quite regular at a rate of 115, at other times somewhat slower and completely irregular. The pulse was small, equal at the two wrists, of low tension. There was moderate thickening of the radial arteries. There were no abnormal venous pulsations discernible in the neck. The liver and spleen were not enlarged, and there was no oedema or ascites.

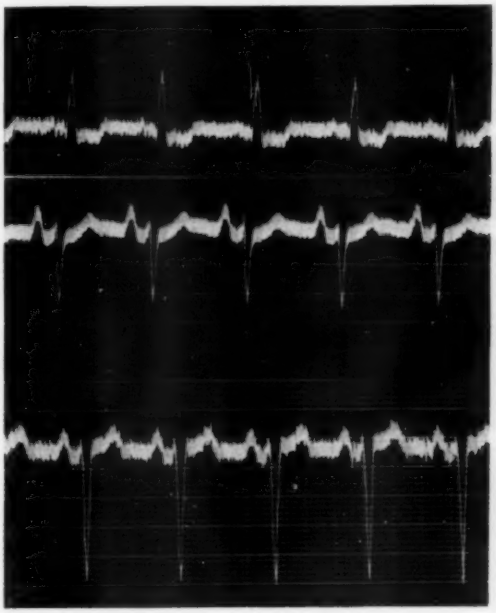

FIG. 12. NORMAL SINUS RHYTHM (CASE 3)

Laboratory tests. Urine: normal. Blood count: normal. Blood Wassermann reaction: negative. X-ray of chest: Lungs clear. Aorta dilated. Cardiac shadow enlarged. Teleo. measurements: M.R. 4.8 cm. M.L. 10 cm. A. 6.8 cm. T. 29.2 cm.

Course in the hospital. The clinical diagnosis of auricular flutter with varying ventricular response was confirmed by electrocardiogram. Two days after admission a single record of auricular fibrillation was obtained, following 0.6 gram of

digitalis, but the following day flutter was again present. On October 15, no further digitalis having been given, records were taken during pressure on the vagus nerves without alteration of rate or rhythm, a regular 2:1 response with auricular rate 240 and ventricular rate 120 being present. The patient then was asked to sit up and lie down in bed alternately twenty times. A record taken immediately afterwards showed a 1:1 response with an auricular and a ventricular rate of 222. The 1:1 response was sustained for groups of from 4 to 10 beats, and then would be interrupted by a single 2:1 response. Five minutes later, 2:1 and 1:1 responses were equally frequent. Eight minutes after exercise, 3:1 response predominated, with one 2:1 and one 1:1 response interspersed. Ten minutes after exercise, a perfectly regular 3:1 response was established, with an auricular rate of 231 and a ventricular rate of 77. A regular 3:1 response had not been observed in this patient previously.

Digitalis in large doses was then started. Ten days after admission he had received a total of 4.3 grams of the powdered leaf. During the last three days of its administration the patient suffered from anorexia, but no other untoward symptoms were noted. A 3:1 response became predominant, although this was not recorded electrocardiographically, since the exertion of going to the Heart Station in a chair decreased the grade of block. Digitalis was stopped on October 20th. The anorexia persisted for five more days, and on October 24th and 25th a high grade of A-V block was established. The ventricular rate was variable, between 50 and 60, and 5:1, 6:1 and 7:1 responses appeared in the electrocardiographic records—apparently a delayed digitalis effect On October 26th, a 3:1 response was again dominant, and two days later small doses of digitalis were started in an effort to prevent further unblocking of the A-V node. On this régime the patient was able to get up for much of the day without mishap.

On November 4th the administration of quinidine sulphate, 2.0 grams a day divided into five doses, was begun; powdered digitalis 0.1 gram a day was continued. On the morning of November 7th, after he had received 6.4 grams of quinidine, he was found sitting contentedly in a chair with a pulse rate of over 200. Electrocardiogram showed 1:1 response at a rate of 222. The paroxysm, which was unaccompanied by unpleasant subjective sensations, subsided in a little more than an hour. Late that afternoon his pulse was regular at 60, increasing to 70 after exercise but remaining regular, indicating a return to normal rhythm. The following morning these observations were confirmed by a record which showed normal sinus rhythm at a rate of 60; the complexes were normal save that R_1 was notched and slurred, suggesting myocardial damage, and that a levogram was present.

The patient was discharged on November 12, having maintained normal sinus rhythm. A few auricular extrasystoles were noted. Since discharge he has continued to take small doses of digitalis and quinidine. When last seen on November 29th he was still somewhat weak and dyspnoeic on exertion; B.P. was 180/90; there were many auricular extrasystoles in the electrocardiogram.

TABLE II

Analysis of electrocardiograms, Case 3

RECORD	DATE	RATE PER MINUTE		RHYTHM	A-V BLOCK	DIGITALIZATION	TOTAL QUINIDINE	REMARKS
		Auricles	Ventricles					
							grams	
1	10/12/32	316	125±	Auricular flutter	2:1 and 3:1	Partial		0.6 gram digitalis given before Record 1 was taken
2	10/13/32	Irregular	85±	Auricular fibrillation		Partial		No further digitalis given until October 16
3	10/14/32	236	118	Auricular flutter	2:1	Partial		
4	10/15/32	238	119	Same	2:1	Partial		
5–7	10/15/32	240	120	Same	2:1	Partial		Pressure on right, left and both vagi produced no alteration
8–12	10/15/32	222	222	Same	1:1	Partial		Immediately after exercise
13	10/15/32	236	98.5	Same	1:1 and 2:1	Partial		5 minutes after exercise
14	10/15/32	231	77	Same	3:1; one 2:1; and 1:1	Partial		8 minutes after exercise
15	10/15/32	231	77	Same	3:1	Partial		10 minutes after exercise
16	10/17/32	230	115	Same	2:1	Partial		
17	10/18/32	222	94±	Same	2:1 and 3:1	Complete		Onset of marked anorexia
18	10/20/32	240	100	Same	Alternate 2:1 and 3:1	Complete		Total of 4.3 grams digitalis since admission; digitalis stopped
19–20	10/24/32	236	55±	Same	3:1 to 7:1	Complete		
21	10/27/32	237	79	Same	3:1	Complete		Maintenance doses of digitalis begun
22	11/ 5/32	218	73	Same	3:1	Complete	2.4	
23	11/ 7/32	222	222	Same	1:1	Complete	6.4	Paroxysm lasting 1 hour
24	11/ 8/32	60	60	Sinus	None	Complete	8.0	
25	11/12/32	88	88	Sinus	None	Complete	9.0	
26	11/28/32	80	80	Sinus	None	Complete	12.2	Many auricular extrasystoles

Summary. A negro laborer of 55, with no history of heart trouble or other serious disease, had a single attack of palpitation ten years before his present illness. For five months before admission to the hospital, moderate exertion precipitated attacks of paralyzing weakness and shortness of breath; there was slight orthopnoea even at rest. On admission he had auricular flutter with a 2:1 and 3:1 response. After a little exercise, 1:1 response was recorded electrocardiographically. Tremendous doses of digitalis were given without serious intoxication; four days after withdrawal of the drug, the ventricular rate became very slow, with frequent 6:1 and 7:1 responses. After 6.4 grams of quinidine had been given a 1:1 paroxysm appeared unassociated with exertion. Later in the day normal sinus rhythm was established and has remained for three weeks.

Comment. This case is a typical example of 1:1 flutter, and includes most of the features discussed in the following section. Table II summarizes the 26 electrocardiograms taken on this patient during the course of seven weeks. Here, as in Case 1, the initial auricular rate is higher than that of subsequent records, while the lowest auricular rate is found during quinidine administration. It is of interest that definite auricular slowing occurred when the ventricular response changed from 2:1 to 1:1 following exercise; whereas the auricles had been beating at 240 with the ventricles at 120, within a few minutes both were contracting at a rate of 222.

REVIEW OF TWENTY-FOUR CASES OF 1:1 FLUTTER

The three cases reported above together with twenty-one additional cases from the literature have been summarized in Table III. Several reported cases have been omitted, either because the diagnosis from the evidence presented is inconclusive (5, 8, 13, 14, 21, 26), or because the references were not available (28, 34). Parkinson and Bedford (22) referred briefly to two additional cases in which 1:1 paroxysms occurred only during the administration of quinidine. In all the cases analyzed in Table III, 1:1 attacks occurred spontaneously. Only one case of 1:1 flutter occurring in infancy is included. Others have been described (4, 12, 15, 32), but as Wilson (33) points out, there is considerable difficulty in differentiating 1:1 flutter from paroxysmal tachycardia in children. He sets forth the following criteria by which the two conditions may be distinguished in adults.

	PAROXYSMAL TACHYCARDIA	AURICULAR FLUTTER
Rate	Below 200	Above 200
A-V Relationship	Always 1:1	Changes from 1:1 to 2:1
Duration	Hours to days	Months to years

The attacks described in infants are of brief duration, but with very rapid rates, frequently as high as 250 to 290. 2:1 block has not been observed except in the case reported by Poynton and Wyllie (24). Wilson concludes that he is unable to classify such arrhythmias accurately, and bestows upon them the special title of "auricular tachysystole."

In Table III, "established flutter" indicates the failure of the arrhythmia to end spontaneously within fourteen days, as defined by Parkinson and Bedford (22); "paroxysmal flutter" denotes briefer attacks. Unless the patient is under continuous observation, the distinction is difficult to make, since the paralyzing attacks described by the patient are often paroxysms of 1:1 response, and the onset or offset of 2:1 or 3:1 response may not be noticed.

There is striking similarity in the evolution of most of the twenty-four cases listed. In two small groups, however, the mechanism is somewhat different. The first group is composed of Cases 5 and 6. In both instances, the paroxysm began with a tachycardia of auricular origin in which there was a rapidly increasing rate; when the rate reached a maximum of 240 and 273 respectively, abnormal ventricular complexes appeared. This was immediately followed by the appearance of 2:1 block. In Case 6, normal sinus rhythm was reëstablished fifteen minutes later, while in Case 5 the auricular rate slowly decreased and finally became exceedingly variable. The identity of the initial stages of these two cases of arrhythmia suggests their relationship. While the sudden transition from ventricular rate of well over 200 to one of exactly half that rate is characteristic of flutter, that is but part of a series of connected events which make up an unusual form of paroxysm.

The second group includes Case 2, possibly Case 10, Case 11 and Case 18, and seems to be closely allied to the "auricular tachysystole" of childhood (*v.s.*). It differs from paroxysmal auricular tachycardia in one respect: the recorded heart rates lie above the upper limit stipulated for the latter arrhythmia, variously put at 200 (33) and 220 (16). No degree of A-V block has been observed in these cases, and save in Case 10, the paroxysms were of relatively brief duration—ten minutes to six days. Whether or not they represent true paroxysmal auricular tachycardia can only be determined by electrocardiograms

TABLE III

Summary of cases of 1:1 flutter

NUMBER	AUTHOR AND DATE	SEX	COLOR	AGE	OTHER EVIDENCE OF CARDIAC DISEASE	ASSOCIATED DISEASES	TYPE OF FLUTTER	OBSERVED A-V RATIOS	DURATION	1:1 RATE	REMARKS
					Cases from Johns Hopkins Hospital						
1	Bedell, 1933	F	C	40	Cardiac enlargement. Congenital heart disease	Exophthalmic goitre	Established	1:1, 2:1, 3:1	8 months	260	Patent foramen ovale found at autopsy
2	Bedell, 1933	F	W	21	None	Puerperal sepsis	Paroxysmal	1:1	4 years	244	Attacks precipitated by excitement or overeating, last 10 minutes to 24 hours
3	Bedell, 1933	M	C	55	None save occasional auricular P.B.	None	Established	1:1, 2:1, 3:1, 4:1 (D), 5:1 (D), 6:1 (D), 7:1 (D)	6 months	222	Suggestive history of single attack 10 years before. Attacks brought on by exertion
					Cases collected from literature						
4	MacKenzie, 1910–1911	M	W	47	None	Mild typhoid fever before onset	Established and paroxysmal	1:1, 2:1, ?3:1	11 years plus	290–300	Diagnosis confirmed by phlebograms. 1:1 attacks precipitated by exertion and defecation; diminished and ceased on NH_4Br. Digitalis restored N.S.R.
5	Parkinson and Matthias, 1915–1917	F	W	20	None	Severe toothache day of onset	Paroxysmal with increasing rate	1:1, 2:1, 3:1, 5:1	1 year plus	225–240	Attacks related to exertion and excitement
6	White and Stevens, 1916	F	W	38	None save occasional auricular P.B.	? TBC 8 years before; bilateral cervical ribs; circulatory disturbance in hands	Paroxysmal with increasing rate	1:1, 2:1	18 months	231–273	Following removal of right cervical rib, which was the larger of the two, attacks of flutter ceased and circulation in hands improved
7	Koplik, 1917	M	W	10	None	None	Established?	1:1, 2:1, 3:1, 3:2	2 months	225	Marked congestive failure during attack

8	Blackford and Willius, 1918	M	W	45	Heart enlarged	Typhoid fever at age of 18	Established?	1:1, 2:1	2 years	224	For two years, attacks of dyspnoea and precordial pain radiating to epigastrium. Worst attacks incapacitating, ½ hour's duration
9	Blackford and Willius, 1918	F	W	32	None	Tonsillitis. Exophthalmic goitre. Biliary colic	Established	1:1, 2:1	Several months	320	During one attack, ventricular rate was 320 for nearly two hours; patient was able to walk several blocks. "Fastest human ventricular rate recorded"
10	Blackford and Willius, 1918	M	W	55	None save occasional auricular P.B.	Subject to "grippe"	Established?	1:1	5 years	224	For 5 years, attacks of syncope, and dyspnoea during weeks or months. 1:1 response during syncope; on vagal pressure, rate slowed to 55 with return of consciousness
11	Blackford and Willius, 1918	M	W	39	None	Hay fever for years; asthma 1 year	Paroxysmal	1:1	1 year	212	Two attacks of tachycardia, lasting 6–8 days; abrupt onset and offset; congestive failure during attacks. No electrocardiograms
12	Scott, 1922	M	W	25	None	Influenzal pneumonia 2 years before in 1918	Established	1:1, 2:1, 3:1 (D), 4:1 (D)	Few months	272	1:1 attacks produced by slight exercise; ended by vagal pressure or by lying flat. Digitalis induced sinus rhythm; no flutter for a year and a half
13	Wedd, 1924	M	W	47	Tympanitic A_2	None	Established	1:1, 2:1	6 weeks, ? 17 years	260	1:1 attacks precipitated by exertion or excitement. For 1 month 17 years ago subject to similar attacks
14	Gallavardin, Bonnamour and Bernheim, 1924	M	W	47	None	Fibroid pulmonary TBC	Established	1:1, 2:1, 3:2	5 months, ?30 years	270	For 30 years, monthly attacks of tachycardia, lasting 10–15 minutes, stopped by holding forced inspiration. For 5 months flutter, not stopped by holding breath. Any effort produced 1:1 response; once fell in street
15	MacMillan and Sweeney, 1925	M	W	57	Syphilitic aortitis with aneurysm	Syphilis	Established	1:1, 2:1	3 weeks plus	260	Attacks of 1:1 response on mild exertion lasting 3–5 minutes
16	Berard, 1926	F	W	?	Mitral stenosis and aortic insufficiency, well compensated	Rheumatism and chorea denied	Established	1:1, 2:1, 3:1, 4:1, 5:1 (D), 6:1 (D), 7:1 (D)	6 months, ?2–3 years	250	1:1 attacks appear on emotion or slight exercise. 5:1–7:1 block produced by digitalis, no 1:1 attacks thereafter

P.B. = premature beat. D = digitalis effect.

TABLE III—*Concluded*

NUMBER	AUTHOR AND DATE	SEX	COLOR	AGE	OTHER EVIDENCE OF CARDIAC DISEASE	ASSOCIATED DISEASES	TYPE OF FLUTTER	OBSERVED A-V RATIOS	DURATION	1:1 RATE	REMARKS
					Cases collected from literature—*Concluded*						
17	Poynton and Wyllie, 1926	M	W	3½	Cardiac hypertrophy	None	Paroxysmal	1:1, 2:1, 3:1	3½ years	250	Frequent attacks of tachycardia since birth; abrupt onset, gradual offset over a period of several days
18	Allen, 1927	F	W	19	Chronic rheumatic endocarditis; mitral stenosis	Left hemiplegia from embolus	Paroxysmal	1:1	6 years	235	Attacks lasted four days, coming at monthly intervals
19	Parkinson and Bedford, 1927	M	W	43	Mitral stenosis and aortic insufficiency	None	Established	1:1, others not stated	5 months	254	Attacks of 1:1 response lasted 20 minutes to two hours. Associated with pain about left nipple and down left arm
20	Parkinson and Bedford, 1927	M	W	55	Arteriosclerosis	Syphilis	?	1:1, others not stated	Unknown	275	Two syncopal attacks from 1:1 response
21	Herapath, 1928	M	W	28	?	None	Established?	1:1, 2:1, 3:1 (D), 4:1 (D)	?7 years	264	Invalided out of army with "disorderly heart action." After 5 years, thought to be well. In next two years, two attacks of flutter
22	Herapath, 1928	M	W	17	None	Arrhythmia started after influenza	Established	1:1, 2:1	8 months	288	1:1 response produced by exercise. No electrocardiogram of arrhythmia
23	Sprague and White, 1928	M	W	49	Slight cardiac enlargement	Migraine	Established	1:1, 2:1, 3:1 (D)	5 years	240	1:1 attacks produced by exertion or emotion, lasted minutes or hours. Once fell to floor at onset. Sometimes could stop 1:1 attack by holding breath in full inspiration
24	Fuller, 1928	M	W	46	Hypertension	None	Established	1:1, 2:1, 3:1	1 year	240	"Weak spells" lasted a few minutes to several hours. At first precipitated by exertion or excitement, later occurred during rest, several times a day. Precordial pain, tremor, sweating, nausea, vertigo, and dyspnoea during attack

of the onset or offset of a paroxysm. Such a record has not been obtained. Until this has been done it seems simpler to classify these few cases with the paroxysmal auricular tachycardias, to which they are much more closely related clinically than to the group described below. Among twenty records of paroxysmal auricular tachycardia taken in the Johns Hopkins Hospital, the heart rate lay between 200 and 210 in two, between 210 and 220 in three, and in one instance was 222.

The remaining eighteen cases constitute a well defined group which may profitably be studied to determine the nature and manner of occurrence of 1:1 paroxysms.

Incidence. The onset of flutter occurred in thirteen out of the eighteen cases between the ages of 32 and 57. The average age of onset was 36 years. In two instances the age of onset is not given; Case 20 was observed in flutter at 55, and Case 16, of unstated age, was a woman with two children of 16 and 12 years. The oldest patient was 57 years, the youngest had attacks from birth. Age incidence is summarized by decades as follows:

	DECADE							
	1	2	3	4	5	6	7	8
Cases (age known)	1	2	2	2	7	2	0	0
Cases (age estimated)					1	1		
	1	2	2	2	8	3	0	0

This is preponderantly a series of middle-aged patients. It differs from an unselected group of flutter cases in that no representatives are found in the 7th and 8th decades of life, whereas 15 of Parkinson and Bedford's 52 cases of auricular flutter were over 60 and two of these were over 70. This suggests an inability of the nodal tissue in elderly individuals to transmit stimuli at a sufficiently rapid rate to permit a 1:1 response. Fifteen of the patients were males and three were females, bearing out the statement made by Lewis (16) that flutter is four times as common in males as in females. Two cases were in negroes; the remaining 16 belonged to the white race. As to the frequency of cases with 1:1 attacks among all patients with auricular flutter, Parkinson and Bedford reported 2 out of 52 cases, to which may be added 2 out of 48 cases of auricular flutter from this

hospital. The resulting incidence of 4 per cent is undoubtedly too low; it is extremely likely that others of these hundred patients had attacks when they were not under hospital observation.

Etiology. There is no evidence that the etiological factors producing flutter in this series differ from those responsible for flutter in general. Briefly listed, the following associated conditions were found: mitral stenosis and aortic insufficiency, 2; syphilitic aortitis with aneurysm, 1; hypertension, 1; cardiac enlargement, 3; tympanitic aortic second sound, 1; auricular extrasystoles, 1; heart apparently normal, 6; exophthalmic goitre, 2. In one instance the arrhythmia started after influenza, in another, after typhoid fever.

Type of flutter in which 1:1 paroxysms occur. 1:1 paroxysms occurred most commonly during the course of established auricular flutter which may have existed for months or years. Five patients (Cases 3, 13, 14, 16 and 21) in whom flutter had been established for from 6 weeks to 18 months gave a history suggesting a period of similar cardiac arrhythmia from 3 to 30 years previously. A 2:1 block was predominant in all of the patients; in only one instance was there spontaneous appearance of cycles of 4:1 block, while in 7 cases only 1:1 and 2:1 responses were observed before the administration of digitalis. In the remainder, a 3:1 response was noted at one time or another.

The 1:1 paroxysm. When 2:1 flutter is first established, the patient is often able to lead a normal life, although he may be conscious of palpitation. After a matter of weeks or months, he may suddenly become the victim of paralyzing attacks of 1:1 flutter, precipitated by any sudden or unusual exertion. While at first they may occur not oftener than once a week, they gradually become more frequent, requiring less and less in the way of exertion or excitement to set them off. They may finally occur daily or oftener, even while the patient is at rest in bed (Case 24). The paroxysm begins abruptly, and may be accompanied by such cerebral anemia that the patient falls to the ground unconscious (Cases 14, 20 and 23). If syncope does not occur, the patient is overwhelmed with great weakness and with extreme shortness of breath, so that he is at once obliged to sit down. These symptoms overshadow the subjective sensation of palpitation so that it may later be overlooked in giving a history of the attack. Pre-

cordial pain may be noted (Cases 8, 19 and 24), radiating to the epigastrium or down the left arm. Tremor, sweating, vertigo, nausea and great mental agitation are frequently felt. Marked congestive failure is not common, but occurred in Case 7. While usually unable to stir during the attack, the patient in Case 9 provides a remarkable exception, since she was able to walk several blocks with a ventricular rate of 320. The paroxysms may last only a few minutes or a number of hours, but in the majority of instances have a duration of 30 minutes to 2 hours. The attack subsides more gradually than it begins; whereas the onset is characterized by an immediate jump from 2:1 to 1:1 response, during the offset the two grades of block are intermingled in all proportions, providing a gradual transition from one heart rate to the other. Most of the attacks end only spontaneously. In Case 12, they could be stopped by vagal pressure or by lying flat. In Case 14 and Case 23, the attacks could at times be aborted by holding the breath in full inspiration.

As stated above, some form of exertion or excitement is usually the precipitative factor in spontaneous paroxysms. During treatment, the refractory state of the A-V node may be so decreased by the action of quinidine that attacks are often noted. Study of Case 1 suggests that atropine and possibly avertin may have a similar effect. The average rate of the ventricles during 1:1 attacks was 259; the slowest rate was 222 and the fastest 320 per minute.

Prognosis. In none of the reported cases did death occur during a 1:1 paroxysm with the possible exception of Case 1, whose heart rate immediately before death is unknown. Theoretically, the risk is greater in this than in other forms of auricular flutter on account of the possibility of syncope and coincident injury. The duration of the attacks is usually insufficient to produce serious congestive failure, but their frequent occurrence must be an additional burden to any already inefficient circulation.

Treatment. Much has been written concerning the relative efficacy and proper use of digitalis and of quinidine in bringing auricular flutter to an end. This is not the place to enter into such a discussion; there are, however, two points which should be especially emphasized in regard to the treatment of patients subject to 1:1 attacks. If digitalis is given in full doses, the refractory state of the A-V node is usually

increased to such an extent that the patient is no longer liable to experience 1:1 paroxysms. Whether or not the flutter can be abolished, this measure alone does much to restore the patient to useful existence. It has been brought out that quinidine enhances the likelihood of occurrence of such attacks. It would therefore seem wise to administer quinidine to patients with 2:1 and 3:1 auricular flutter only if they can be kept at bed rest during the therapeutic course.

SUMMARY

1. Paroxysmal attacks of 1:1 response occurring during the course of auricular flutter are described in twenty-four cases. Three of these cases are reported for the first time, with electrocardiograms and tabulated analysis of the records obtained; the remaining twenty-one cases have been gathered from the literature.

2. The twenty-four cases have been subdivided into three groups in which the mechanism seems somewhat different: (a) Two cases characterized by rapidly increasing auricular tachycardia in which 2:1 block appears shortly after a rate of 240–273 is reached. (b) Four cases resembling paroxysmal auricular tachycardia, but with heart rates ranging from 212 to 244. There is no definite evidence that these are instances of auricular flutter. (c) Eighteen cases, forming a unified group, from which the characteristics of 1:1 flutter were adduced.

3. 1:1 flutter occurs most frequently in the fifth decade of life; it has not been observed above the age of 57, in contrast to other forms of auricular flutter, which may occur after the age of 70. In other respects, the etiology is not dissimilar.

4. 1:1 paroxysms occur during the course of established auricular flutter in which a high grade of block is not established, often with increasing ease and frequency.

5. The attack begins abruptly following exertion. Extreme weakness, shortness of breath and palpitation are the usual manifestations. Syncope, precordial pain and congestive failure may occur. After minutes or hours, the attack subsides gradually.

6. Attacks have followed the administration of quinidine, as well as the combination of atropine and avertin.

7. The attacks of syncope and possibility of congestive failure during frequent paroxysms somewhat modify the general prognosis in flutter.

8. Digitalis effectively prevents 1:1 paroxysms by increasing the A-V block. During quinidine administration the patient should be kept in bed on account of the possibility of paroxysms.

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